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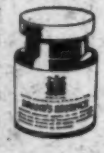

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 31 1951

PENICILLIN-RESISTANT SUBACUTE BACTERIAL ENDOCARDITIS TREATED BY A COMBINATION OF PENICILLIN AND STREPTOMYCIN

BY

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In subacute bacterial endocarditis the choice of treatment depends upon the sensitivity of the infecting organism to antibiotics. Fortunately most of these organisms are sensitive to penicillin, when two million units of penicillin daily for four to six weeks can be expected to eliminate infection. In about 1% of cases, however, the infecting organism is highly resistant to penicillin, growth being uninhibited by less than 1 unit of penicillin per ml.; and then enormous amounts of penicillin may fail to eradicate the disease. As these cases are rare the best methods of treatment cannot be decided by adequate clinical trials and can be deduced only from reports on small groups or even single cases. In the past year we have treated four patients in whom the infecting organisms were resistant to penicillin, growth being inhibited by 4, 3, 4, and 4 units of penicillin per ml. respectively. Various courses of antibiotics were given, and of these the combined use of penicillin and streptomycin seemed to be the best. This form of treatment was first advocated by Hunter (1947) and has since been proved of value by Robbins and Tompsett (1949), but it has not yet been reported in this country. Laboratory studies with the infecting organisms in two of our cases have shown that the bactericidal action of penicillin was enhanced by the addition of streptomycin but was partially inhibited by the addition of "aureomycin."

Case 1

A married woman aged 36 was transferred to this hospital in January, 1950. Seven months previously, when four months pregnant, she aborted; this was followed by femoral thrombosis and an empyema from which was grown *Staphylococcus aureus*. The patient was given penicillin and became convalescent. Two months before admission she had a cerebral embolism, and blood culture grew a "micrococcus resistant to penicillin and sensitive to streptomycin." Streptomycin, 2 g. daily, did not control the infection, and the organism became resistant to streptomycin.

On admission the patient was wasted and was in early heart failure. She had signs of mitral-valve disease with subacute bacterial endocarditis, and there was a left-sided hemiplegia. Blood culture yielded *Streptococcus faecalis*, the growth of which was inhibited by 4 units of penicillin, 30 μg. of streptomycin, 20 μg. of chloramphenicol, and 0.15 μg. of aureomycin per ml.

Aureomycin, 2 g. daily, was given for six weeks. During this time fever was reduced from 101 to 99° F. (38.3 to 37.2° C.); blood culture was positive on the third and sixth days, and became negative thereafter. However, six days after the end of this course of treatment fever rose to 101° F. and blood culture was again positive. Sensitivity of the organism to aureomycin had not changed.

Aureomycin, 2 g., and 20 million units of penicillin were then given daily. Once more the fever fell to about 99° F., but the patient lost her appetite and vomited, became weak, listless, and mentally confused. Aureomycin was therefore stopped after 15 days; penicillin alone was given for the next two days. Blood culture taken at that time was negative. Streptomycin, 4 g., was then given with the daily dose of 20 million units of penicillin, and this combined treatment was continued for six weeks. The patient's appetite returned and she improved mentally, but her muscle at the sites of injection became indurated and painful, and heart failure slowly increased. After this course of treatment she was afebrile except for one spike of 99.4° F. (37.4° C.). Blood cultures were negative. She died from heart failure 17 days after treatment ended, and culture of the heart valves grew contaminants only; organisms were seen in sections of the vegetations, but most of them stained badly and were pleomorphic.

Comment. — Although the growth of infecting organisms was inhibited by 0.15 μg. of aureomycin per ml., infection returned after a six-weeks course of 2 g. a day. The infection was apparently controlled while aureomycin and penicillin were given together, but aureomycin had to be stopped because the patient became intolerant of it. Streptomycin and penicillin given together likewise apparently controlled the infection, and infection did not return in the 17 days that the patient survived.

Case 2

A man aged 57 was transferred to this hospital in March, 1950. Nine months previously subacute bacterial endocarditis had been diagnosed; the infecting organism was *Str. faecalis*, and its sensitivity to antibiotics was similar to that found later. The following courses of treatment failed to eliminate infection: 1.8 million units of penicillin daily for one month; 2 g. of streptomycin daily for two weeks, increased to 3 g. daily for one week; 0.5 g. of aureomycin for one day, 2 g. daily for a week, 4 g. daily for 13 days, increased finally to 8 g. daily for one month. (Each increase in dosage was made because low-grade fever appeared.)

On admission the patient was fibrillating; he had aortic-valve disease with signs of subacute bacterial endocarditis. There was no heart failure and he was not wasted.

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Blood culture yielded *Str. faecalis*, the sensitivity of which to antibiotics was as follows:

	Minimum Inhibitory Concentration (per ml.)	Maximum Concentration Allowing Growth (per ml.)
Penicillin	3 units	2 units
Streptomycin	30 μg.	10 μg.
Chloramphenicol	6 μg.	3 μg.
Aureomycin	0·1 μg.	0·05 μg.

Twenty million units of penicillin, 24 g. of "caronamide," and 2 g. of aureomycin were given daily. His temperature fell from 100° to 97° F. (37.8 to 36.1° C.) within 24 hours, but rose again between the eighth and twelfth days to 102° F. (38.9° C.). Aureomycin was therefore stopped and penicillin with caronamide was continued for two days. Fever persisted, but blood culture taken at that time was negative. Streptomycin, 4 g., was then given with the penicillin and caronamide, and this combined treatment was continued for seven weeks. His temperature fell to normal in five days, and blood cultures remained negative. The patient was alive and free from infection six months later, though vestibular damage interfered with his walking and he had early heart failure.

Comment.—Although the infecting organism was sensitive to 0.1 μg. of aureomycin per ml., infection returned after a seven-weeks course, including 8 g. daily for one month. When aureomycin and penicillin were given together fever was not controlled. After a combined course of penicillin and streptomycin, infection has apparently been controlled.

Case 3

A man aged 41 was admitted into this hospital in October, 1950. In January, 1946, he had had subacute bacterial endocarditis with a right-sided hemiplegia. The underlying lesion was rheumatic heart disease affecting both the aortic and the mitral valves. The infecting organism was a *Str. viridans* three times more sensitive to penicillin than the Oxford H staphylococcus. The patient was given 500,000 units of penicillin daily for a month, and recovered. In October, 1946, three infected teeth were removed under an umbrella of 500,000 units of penicillin daily for five days without untoward effect. In January, 1949, six more teeth were removed under an umbrella of 600,000 units of procaine penicillin daily for three days, again without untoward effect. In August, 1950, he was once more admitted for dental extraction; there was some gingivitis, but no evidence of bacterial endocarditis, and he had no fever and the E.S.R. was 6 mm. in one hour. Penicillin, 500,000 units, was given every six hours from 7 p.m. on August 29 to September 4. Five teeth were extracted on August 31 and five more on September 2. The gums healed naturally, and the patient was discharged on September 6 with no fever and an E.S.R. of 11 mm. in one hour.

At a follow-up five weeks later he was found to have signs of subacute bacterial endocarditis. He had become thinner; although he was afebrile, his E.S.R. was 42 mm. in one hour, and blood culture grew *Str. viridans*. The organism was highly resistant to penicillin, growing in 2 units but being inhibited by 4 units of penicillin per ml. It was almost completely inhibited by 3 μg. of streptomycin per ml.

The patient was admitted at once and was given 2 million units of penicillin daily while the resistance of the organism was being measured. Blood culture taken during this time was found to be positive. He was then given 4 g. of streptomycin and 20 million units of penicillin daily for six weeks. During this course his temperature rose to 100° F. (37.8° C.) and his E.S.R. remained raised, between 22 and 38 mm. in one hour. He developed a slight lumbar pad of oedema but no other evidence of heart failure, and this oedema was in part due to the repeated intramuscular injections. At the end of treatment the function of both labyrinths was destroyed. The patient was alive and free from infection three months after the end of treatment.

Comment.—A second attack of bacterial endocarditis followed dental extraction in spite of an umbrella of 2 million units of penicillin daily for six days. The organism, a *Str. viridans*, was highly resistant to penicillin but relatively sensitive to streptomycin. The patient was apparently cured by 20 million units of penicillin and 4 g. of streptomycin daily for six weeks.

Case 4

A man aged 63 was transferred to this hospital in January, 1951. Five years previously, in 1945, he developed subacute bacterial endocarditis, and *Str. viridans* was isolated from the blood. Penicillin, 500,000 units a day for four weeks, apparently eliminated the infection and he remained well until July, 1950, when after prostatectomy he became febrile and *Str. faecalis* was found in blood culture. He was given penicillin and streptomycin for about three weeks; details of this course of treatment are not available, but the daily dose was probably small. A week later blood culture was again found to be positive. He then received a long course of penicillin and streptomycin: an average daily dose of 16 million units of penicillin was given for six weeks, and during the first 19 days he also received an average daily dose of 2.5 g. of streptomycin. During the last three weeks of this course the patient was afebrile, but fever then returned and blood culture again became positive. The patient was then given chloramphenicol for 10 weeks, with an average daily dose of 3.8 g.; even when the daily dose was as high as 7 g. a day he remained febrile and the blood culture positive. Three days after the end of the last course he was admitted to this hospital.

On admission the patient had a rough systolic mitral murmur with signs of subacute bacterial endocarditis. He was not wasted and there was no evidence of heart failure.

Blood culture yielded *Str. faecalis*, and its sensitivity to antibiotics was as follows:

	Minimum Inhibitory Concentration (per ml.)	Maximum Concentration Allowing Growth (per ml.)
Penicillin	4 units	2 units
Streptomycin	125 μg.	62·5 μg.
Chloramphenicol	2·5 μg.	1·25 μg.
Aureomycin	0·15 μg.	0·07 μg.

Five days after admission the patient developed a severe anterior myocardial infarction. Three days later 20 million units of penicillin and 4 g. of streptomycin were given daily; the serum levels were 128 units of penicillin and 64 μg. of streptomycin per ml. The temperature promptly fell to normal and remained there, and blood culture was sterile. But the patient rapidly developed heart failure, from which he died five days after treatment began. At necropsy there were large vegetations on the mitral valve and extensive myocardial infarction due to a septic embolus in the left coronary artery. Cultures from the vegetations and from the myocardial infarct yielded *Str. faecalis*.

Comment.—A second attack of subacute bacterial endocarditis followed prostatectomy. Infection returned after two combined courses of penicillin and streptomycin; but the dosages were smaller than those used in the other three cases. Chloramphenicol failed to control the infection. The organism was highly resistant to streptomycin, and, although a third combined course of penicillin and streptomycin promptly controlled the fever, the patient died from heart failure after five days. An organism similar to that causing the original infection was cultivated at necropsy.

Laboratory Observations

The strains of streptococcus from Cases 1, 2, and 4 were typical enterococci (*Str. faecalis*). They were oval cocci forming only short chains; they fermented

mannite, resisted heating to 60° C., and reacted with Lancefield's Group D serum. That from Case 3 had none of these characters and is classified as *Str. viridans*.

The sensitivities of these organisms to single antibiotics have been mentioned. Studies were also made of the action of pairs of antibiotics on some of them. The streptococcus from Case 1 was highly sensitive to aureomycin, and it seemed promising to combine this drug with penicillin. When both were added to broth in concentrations round about their lower individual limit of efficacy for inhibiting growth there was a slight additive effect. When, on the other hand, such cultures were not merely observed for presence or absence of growth after one to two days, but were subjected to viable counts at intervals of 2, 4, 6, 8, and 24 hours, a different picture was obtained. Penicillin alone (50 units/ml.) produced a steady fall in the number of survivors; aureomycin alone (5 μg./ml.) kept the population stationary: the two together had a merely intermediate effect, the death rate being slower than that produced by penicillin only. Similar results were obtained later with the streptococcus from Case 4, using penicillin (10 units/ml.) and aureomycin (5 μg./ml.). They were also obtained with a more sensitive organism, the Oxford H staphylococcus; penicillin, 0.1 unit/ml., caused a 99.99% mortality in eight hours; aureomycin, 0.3 μg./ml., kept the count almost constant: the two together caused a mortality of only 96%.

It was thus evident that, whatever the ultimate fate of the organisms, aureomycin reduced the rate at which they were killed by penicillin. On the other hand, streptomycin, which is itself bactericidal and not merely bacteriostatic, increased it. In an experiment with the streptococcus from Case 1, penicillin, 10 units/ml., caused a mortality of about 99.99% in eight hours; streptomycin, 10 μg./ml., had the same effect in four hours: the two drugs together reduced survivors to this level in between two and three hours. Even in a concentration itself sub-inhibitory, streptomycin accelerated the action of penicillin. This was shown with the streptococcus from Case 4: this organism was not inhibited by 50 μg. of streptomycin per ml. and slow growth occurred in this concentration. When it was added to medium also containing 10 units of penicillin per ml., the number of survivors at each time interval was smaller than in medium containing this amount of penicillin alone, the difference varying from about fourfold at four hours to thirtyfold at 24 hours.

These results correspond with those recently reported for combinations of antibiotics by Jawetz and his colleagues which are discussed below. In view of the thorough and decisive nature of their observations it seems unnecessary to describe our own in detail, or to pursue them further than they were carried at the time to give guidance for the treatment of individual patients.

Discussion

When the infecting organism is sensitive to penicillin the best form of treatment is penicillin alone. When the infecting organism is resistant to penicillin large amounts of penicillin may succeed, either when given alone (Hunter, 1946) or when given with some substance that delays penicillin excretion (such as caronamide) (Loewe, Rosenblatt, and Alture-Werber, 1946; Grossman, Feldman, Katz, and Brams, 1947; Hagedorn and Scheifley, 1948; Leaman, Wikingsson, Webster, and Shaw, 1949; Stuart-Harris, Colquhoun, and Brown, 1949); and therefore, although failures have also been reported (Zeller, Hirsh, Dowling, Hussey, and Robinson, 1948; Cates, 1949), it is possible that the success of penicillin combined with streptomycin in Cases 1, 2, and 3 might have been achieved by the same amounts of penicillin alone.

Streptomycin will sometimes succeed in penicillin-resistant infections (Priest and McGee, 1946; Paul, Bland, and White, 1947; Massell, Zeller, Dow, and Harting, 1948; Pearsall, Pillow, and Wood, 1948; Naegele, 1949), but in only 4 of the 18 cases analysed by Hunter could streptomycin be said clearly to have cured the patient. The resistance of the infecting organisms to streptomycin is of great importance, and of the 18 cases reviewed by Hunter (1947) " treatment was not successful in any case in which the organism required more than 8 μg. per ml. for *in vitro* inhibition of growth "; Naegele, however, reported one success with an organism that needed 16 μg. per ml. to inhibit its growth. In our Cases 1 and 2 not only were the infecting organisms relatively resistant to streptomycin, needing 30 μg. per ml. to inhibit growth, but also in each a course of streptomycin failed to eliminate infection; therefore the apparent control of infection that was achieved by a combined course of penicillin and streptomycin can hardly be attributed solely to the streptomycin in that course.

More recently aureomycin has been tried in penicillin-resistant infections, including *Str. faecalis*, micro-aerophilic streptococci, and penicillin-resistant *Str. viridans*; but results have been disappointing, for of 10 patients reported by various authorities (Brainerd, Lennette, Meiklejohn, Bruyn, and Clark, 1949; Harvey, Mirick, and Schaub, 1949; Dowling, Lepper, Caldwell, Whelton, and Sweet, 1949; Schoenbach, 1949) aureomycin failed to cure infection in six, and clearly succeeded in only two. Likewise, in Cases 1 and 2 infection returned after treatment with aureomycin, although the organisms in both were sensitive to this antibiotic.

In 1946 Hunter reported an infecting organism which was resistant to penicillin and streptomycin separately but sensitive to the combination of these two drugs; the patient was cured by a daily dose of 4 million units of penicillin and 4 g. of streptomycin. In 1947 he advised that the combination should be used if the infecting organism showed some sensitivity to both antibiotics, and the success of this treatment has been confirmed by his own experience since then (Hunter, 1950, personal communication), although his penicillin dosage has been increased to about 10 million units daily. Robins and Tompsett (1949) gave a daily dose of 6 million units of penicillin and 2 g. of streptomycin (or dihydrostreptomycin) to six patients with enterococcal bacteriaemia (five with subacute bacterial endocarditis); four patients were apparently cured and the other two died during treatment. They made *in vitro* studies of the combined effect of these antibiotics, and reported that the effect of mixing the two was at least that of summation; however, they studied the bacteriostatic and not the bactericidal effect of combining the two drugs.

Robbins and Tompsett (1951) have subsequently described in detail a total of eight cases of penicillin-resistant streptococcal endocarditis (including those previously referred to). Their experience, more extensive than our own, tallies closely with it. It seems that

enterococcal endocarditis is apt to occur in elderly men, often as the result of lesions of the urinary tract, or in younger women, in whom a common source of infection is the uterus. Penicillin was demonstrably ineffective in controlling these infections, as was aureomycin in one case. On the other hand, combined treatment with penicillin and streptomycin succeeded in eliminating the infection in every case in which a full course was given, and five patients made a complete recovery, including one infected with a streptococcus having the penicillin-resistance of an enterococcus but not its other characters. Their three fatal cases had highly unfavourable features, and death occurred early during treatment in two of them.

The laboratory findings reported here indicate that the bactericidal effect of combining penicillin and streptomycin is more than additive, and thus afford a rational explanation for the success of treatment with this combination of drugs. It has similarly been shown that aureomycin impairs the bactericidal action of penicillin, at least over a limited period of time. We owe the conception of these experiments to the paper by Jawetz, Gunnison, and Coleman (1950), which became available to us while Case 1 was under treatment: in this they showed that penicillin and streptomycin act synergically on enterococci, but chloramphenicol reduces the bactericidal activity of penicillin. It seems likely that aureomycin would behave similarly, and this we found to be so.

Jawetz and his colleagues have since extended their original observations: Jawetz and Gunnison (1950) analyse the reactions of enterococci and viridans streptococci to penicillin and streptomycin; Jawetz and Speck (1950) report that chloramphenicol interferes with the curative action of penicillin on *Str. pyogenes* infection in mice; more recently Gunnison, Coleman, and Jawetz (1950a, 1950b) have further examined the effect of combinations of antibiotics on enterococci and other organisms, and shown that both aureomycin and terramycin behave like chloramphenicol in reducing the rate of killing by penicillin. The full clinical significance of this work remains to be assessed, but it seems possible, as suggested in the *British Medical Journal* (1950), that any combination of a bacteriostatic with a bactericidal antibiotic of the penicillin type may prove inefficient, because the latter can act only on multiplying bacteria.

The development of subacute bacterial endocarditis after dental extraction is not always prevented by prophylactic penicillin, and there are at least five failures in the literature (Glaser, Dankner, Mathes, and Harford, 1948). Case 3 is of particular interest for two reasons. First, the dose of 2 million units daily for six days is so far the largest dose that has failed to prevent bacterial endocarditis. Secondly, Perrin Long (1950, personal communication) observed that it was unwise to give penicillin for an appreciable time *before* dental extraction, because the bacterial flora of the mouth rapidly became penicillin-resistant; the danger of this is supported by our experience, because the patient's teeth were removed in two sittings, the second on the fourth day of the prophylactic course. Although it seems likely that in this case prophylactic penicillin actually induced an endocarditis more formidable than that against which it was expected to guard, it is only fair to observe that there was no comparable case in the whole M.R.C. series of 442 patients (Cates and Christie, 1950), many of whom had dental extraction at the end of long courses of penicillin.

Summary

Four patients are reported with subacute bacterial endocarditis due to penicillin-resistant organisms, three being enterococci.

Courses of streptomycin and of aureomycin were given to two and a course of chloramphenicol was given to a third, all without success. The combination of penicillin and aureomycin failed to control the fever in one and produced toxic symptoms in another.

In three the infection was apparently controlled by a combination of 20 million units of penicillin and 4 g. of streptomycin daily for at least six weeks. One of these patients died later from heart failure; the other two are alive and well, apart from vestibular damage. The fourth patient died from heart failure on the fifth day of treatment, and although clinical response was prompt necropsy indicated that infection had not been eliminated; previously this patient had relapsed after smaller dosages of penicillin and streptomycin given together. The infecting organism was highly resistant to streptomycin.

In vitro, the bactericidal action of penicillin on the two organisms so tested was accelerated by the addition of streptomycin and retarded by the addition of aureomycin.

In one patient tooth extraction during the prophylactic use of 2 million units of penicillin daily for six days was followed by subacute bacterial endocarditis due to a penicillin-resistant organism.

We are glad to acknowledge the kind co-operation of Dr. H. K. Meller in Case 2, and of Dr. R. S. Swindell and Dr. Kenneth Robertson in Case 4. Our thanks are also due to Drs. William C. Robbins and Ralph Tompsett, of Cornell University Medical School, New York, for their kindness in enabling us to read their forthcoming paper before its publication. We are indebted to Miss P. M. Waterworth for technical assistance.

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CLINICAL TRIALS OF A.C.T.H. IN HAEMOLYTIC ANAEMIA

BY

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Gardner (1950) has reported three cases of acquired haemolytic anaemia treated with 60–100 mg. of A.C.T.H. daily. One case showed a decrease in the osmotic and mechanical fragility of the red blood cells to normal, with a fall in the Coombs titre. Transfusions became unnecessary. Similar but less marked improvement was noted in the other two patients. Two of the patients responded to a second course of A.C.T.H. Gardner concluded that the hormone seemed to be temporarily effective in suppressing agglutinins and haemolysins active against the patient's own cells.

Dameshek (1950) refers to two patients with acquired haemolytic anaemia associated with generalized lymphosarcoma who showed striking improvement on A.C.T.H., with a fall in bilirubin and the antibody content of the serum, and an improvement of the lymphosarcomatous process. Relapse followed cessation of treatment, but improvement occurred with the institution of maintenance therapy. He also describes two other patients with acquired haemolytic anaemia who failed to respond to splenectomy but improved during the administration of A.C.T.H. In all four cases no further blood transfusions were required, although previously many transfusions had been necessary to maintain the blood counts at reasonable levels.

It is the purpose of this communication to report the results of the administration of A.C.T.H. in three cases of haemolytic anaemia.

Case 1

The patient, a married woman aged 30, had no family history of jaundice. Her parents, four brothers, and two sisters are alive and well. Her only child is healthy. She had never been seriously ill until 1948, when she developed "pneumonia." Penicillin and sulphonamides were given, and she was confined to bed at home for approximately three months on account of weakness, palpitations, and dyspnoea on effort. About this time she first complained of pain and swelling of the wrists and hands. She was referred to hospital as an out-patient, and a diagnosis of rheumatoid arthritis was made. The highest recorded blood sedimentation rate at this time was 87 mm. in one hour, but no records of the haemoglobin level or red cell count are available. The Wassermann reaction was negative. She received weekly injections of polyvalent vaccine throughout the following year. Her hands and wrists continued to trouble her, but, apart from occasional stiffness of the knees, no other joints were affected. She received two injections of gold, but the drug was stopped on account of albuminuria. Breathlessness and generalized weakness persisted.

She first came under our care when she was referred to the rheumatic clinic on May 28, 1950. Examination then revealed soft swellings on the dorsum of both wrists and hands, but the appearances were not typical of rheumatoid arthritis, and radiological examination was negative. The patient was pale and distressed. The haemoglobin level was 59% (Haldane). She was admitted to hospital nine days later. In the interval her condition had deteriorated. Breathlessness and pallor were much more pronounced, and jaundice had now appeared.

Examination revealed impairment of air entry at the left base. Radiological examination showed inflammatory changes at the left base consistent with a resolving pneumonia. The spleen could not be palpated, but there was tenderness in the left subcostal region. The liver was not enlarged, and there was no lymphadenopathy. The results of the laboratory and haematological investigations are shown in the accompanying Chart. Peripheral blood films revealed poorly filled red cells, anisocytosis, poikilocytosis, and occasional normoblasts. No abnormal white cells were noted. Sternal puncture showed a very active normoblastic marrow. Partial haemolysis of red cells occurred in 0.6% saline, and was complete in 0.5% saline. The direct van den Bergh reaction was negative, the icteric index 15 units, and serum bilirubin 1.6 mg. per 100 ml. The patient's

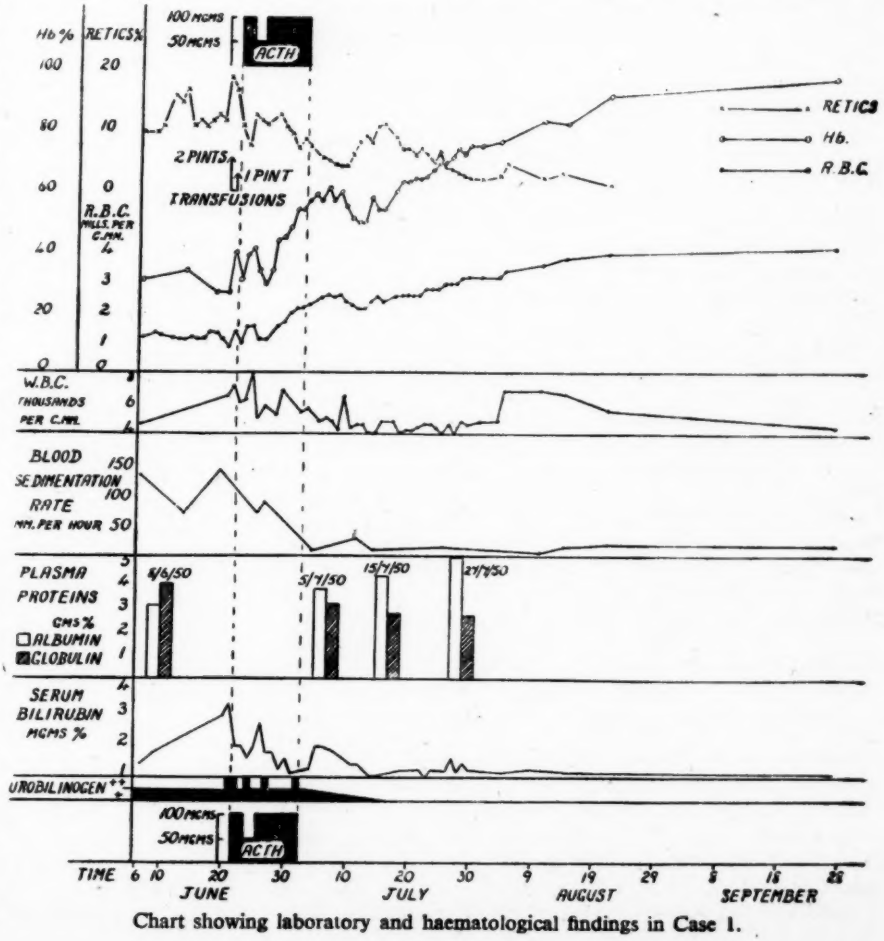

Chart showing laboratory and haematological findings in Case 1.

red cells were strongly agglutinated when suspended in her own serum, in normal serum, and in normal saline. Agglutination remained stable up to a temperature of 50° C. At this point it was dispersed and did not reappear on cooling. After agglutination of the patient's cells in saline had been dispersed by heat, the suspension was stored overnight in the ice-chest. The degree of haemolysis which had taken place at the end of 24 hours was compared with that in a suspension of normal cells in saline which had been heated and stored in the same way. Haemolysis of the patient's cells was almost complete, whereas in the preparation of control cells haemolysis was minimal. Washing the patient's cells did not materially alter agglutination in saline or the degree of haemolysis in the test described. The results of the direct anti-human globulin tests (Coombs) were difficult to interpret because of the agglutination and subsequent haemolysis. The Kahn test was strongly positive. The patient's clinical condition deteriorated as indicated by increasing dyspnoea, rising pulse rate, and the appearance of peripheral oedema. The signs of active haemolysis became more evident; reticulocytes rose, and there was a further fall in the haemoglobin level. Accordingly a total of 3 pints (1.7 litres) of packed cells was given. The beneficial effects were very transient.

On June 22, 1950, A.C.T.H. was administered in doses of 100 mg. daily (25 mg. four times a day). The patient was put on a low-salt diet in view of the possibility of salt and water retention. There was a dramatic improvement in her general condition within a few hours. Tenderness in the splenic region disappeared, dyspnoea became less troublesome, joint pain and swelling diminished, and appetite improved. On the morning of the third day the haemoglobin level had risen from 32% to 40% and the serum bilirubin had fallen from 3.2 mg. to 1.8 mg. per 100 ml. At this point the daily dose of A.C.T.H. was reduced to 50 mg. There was a prompt fall in haemoglobin level and a rise in reticulocytes and serum bilirubin (see Chart). The direct eosinophil count rose, indicating that the dose of A.C.T.H. was no longer sufficient to produce maximum adrenal response.

An increase of the daily dose to 100 mg. again produced a marked improvement in the patient's condition. This dose was continued for seven days. A few days after A.C.T.H. was stopped signs of haemolysis returned, as indicated by a rise in reticulocytes and serum bilirubin, with a fall in the red cell count. These signs quickly disappeared without further treatment, and progress thereafter was uninterrupted. Radiological examination showed that the inflammatory changes previously present at the left base had disappeared. No evidence of relapse had appeared when the patient was last seen on January 24, 1951.

During the period of improvement which followed the course of A.C.T.H. (July 25 to September 28) the following changes were noted. (1) The plasma proteins, which were reversed before the administration of A.C.T.H. (albumin 3 g. %, globulin 3.75 g. %), returned to a normal pattern (see Chart). (2) Agglutination of the patient's cells by her own serum persisted, but it became possible to prepare stable suspensions of her cells in normal serum and normal saline. After agglutination had been dispersed by heating to 50° C. the degree of haemolysis present, after 24 hours in the ice-chest, was comparable to that present in a suspension of normal cells in normal serum treated in the same manner. (3) The direct Coombs test became clearly positive, and the indirect test weakly positive. A weak non-specific cold agglutinin could be demonstrated.

The patient was discharged 54 days after admission completely free from symptoms. She was still well one month later and there had been a further improvement in the blood picture. Coombs's test was still positive, but there was minimal evidence of abnormal antibodies.

The patient was last seen on January 24, when she was in excellent health. Both the Coombs and Kahn tests were negative and all trace of abnormal antibodies had disappeared. The blood figures were: haemoglobin, 83%; R.B.C., 4,200,000; reticulocytes, 2%; serum bilirubin, 0.5 mg. per 100 ml.; E.S.R., 20 mm.

Case 2

The patient was a schoolboy aged 15. At the age of 5 years he had been admitted to the Royal Hospital for Sick Children, Edinburgh, with severe acute haemolytic anaemia, diagnosed as Lederer's anaemia. This responded to blood transfusions, and thereafter he remained well for eight years, until January, 1949, when, at the age of 13, he was admitted to the Royal Infirmary of Edinburgh with pallor, dizziness, vomiting, and night sweats of some two weeks' duration. At this time the haemoglobin was 52%, red cells 2,300,000 per c.mm., white cells 3,500 per c.mm., reticulocytes 6%, and there was a slight increase of the fragility of the red cells to hypotonic saline. A diagnosis of haemolytic anaemia was made.

From his history of previous illnesses it emerged that he had had operations for congenital hypertrophic pyloric stenosis at the age of 5 weeks, and for tonsillectomy and the removal of a tuberculous gland from the left side of the neck at the age of 2 years.

He was first seen by us in April, 1949, when he attended the blood clinic at the Royal Infirmary of Edinburgh. He now complained of dyspnoea on exertion, and his haemoglobin level varied between 74% and 91%. He was admitted to Professor Davidson's ward of the Royal Infirmary in October, 1949. There was no clinical icterus at this time, and the serum bilirubin was 1.3 mg. per 100 ml. The liver was not palpable, and the spleen was enlarged only to percussion. There was a slight increase in the fragility of the red cells to hypotonic saline, haemolysis beginning in 0.5% sodium chloride. The urinary urobilinogen was increased to 14.5 mg. a day and the faecal urobilinogen to 666 mg. daily. The bone marrow was normoblastic, and microspherocytes were present in the peripheral blood. Reticulocyte counts varied from 5% to 7%. The Wassermann reaction was negative.

The boy's parents and his brother gave no history of jaundice or of anaemia, and blood examinations revealed no abnormality. The paternal grandmother, who died in 1947, was said to have suffered from repeated attacks of jaundice.

Despite the lack of a definite family history, a diagnosis of congenital acholuric jaundice was made because of the presence of increased red-cell fragility and microspherocytosis, and the history of haemolytic crises in childhood. Accordingly splenectomy was advised, and the operation was successfully performed by Sir James Learmonth in January, 1950. The spleen weighed 290 g., and histological examination revealed evidence of moderately excessive blood destruction.

Unfortunately, however, no haematological improvement ensued, and the patient was readmitted to Professor Davidson's ward in September, 1950, with a haemoglobin level of 68%, erythrocytes 2,800,000 per c.mm., reticulocytes 4.8%. The marrow was normoblastic, and a differential count of the cells in the peripheral blood showed neutrophils to be 70%, lymphocytes 10%, and monocytes 20%. He continued to be dyspnoeic on exertion, and slight icterus was present. The liver was not palpable, but discrete glandular enlargement was found in the neck, groins, and axillae. Although the enlargement was only slight a gland was removed from the left side of the neck. The pathologist reported that there was reticulo-endothelial hypertrophy in the follicles, and infiltration of the sinuses with endothelial and round cells. The finding was compatible with chronic lymphadenitis or possibly a reticulo-endothelial hypertrophy following splenectomy. The Paul–Bunnell reaction and Kahn tests were negative, as was the direct Coombs test. There was no evidence of "cold" or other abnormal agglutinins as judged by the incubation of the patient's serum with standard cells suspended in saline and in 20% albumin at 4° C., room temperature, and 37° C.

TABLE I.—*Haematological Observations in Case 2, Treated with A.C.T.H.*

Date	Hb (%)	R.B.C. (Mill./c.mm.)	W.B.C. (per c.mm.)	Retics. (%)	Eosinophils. Lowest Daily Count (per c.mm.)	Red Cell Osmotic Fragility: Strength of Saline in which Haemolysis Began	Serum Bilirubin mg./100 ml.	Treatment with A.C.T.H.
26/10/50	73	3·14	10,800	7·4				
27/10/50				7·1				
28/10/50				6·8				
30/10/50	74	3·09	8,800	5·9				
31/10/50				5·0		0·48%	2·3	
1/11/50				5·5	413		2·1	
2/11/50	73	3·17	7,800	5·8	337	0·5%	2·1	
3/11/50				7·4	293	0·5%		
6/11/50	76	3·12	7,800	6·4	144		1·0	40 mg. b.d.
7/11/50			9,800	6·6	150	0·5%	1·0	40 ,, ,,
8/11/50	71		10,800	5·1	163		1·2	40 ,, ,,
9/11/50	74	2·95	13,200	6·8	25	0·5%	1·7	40 ,, ,,
10/11/50				7·6	19			40 ,, ,,
11/11/50	73		13,400	6·1				40 ,, ,,
13/11/50	76			8·2			1·7	
14/11/50				7·4		0·5%	1·5	
15/11/50	80	3·65	9,600	6·2	281		1·5	
23/11/50	78	3·46	8,600	5·8		0·5%		
11/1/51	73	2·82	14,800	4·7			2·3	

It was decided to treat the patient with A.C.T.H., and 40 mg. was given twice daily for six days. The various findings before and after treatment are given in Table I.

The effect of A.C.T.H. on the blood picture may be summarized as follows. It caused a marked fall in the eosinophil count, a rise in the total white cell count, and a moderate increase in the red cell count. Within a few days of the cessation of A.C.T.H. administration, all these findings had returned to the pre-treatment levels. The effect of A.C.T.H. on the haemolytic process was negative as judged by the failure to reduce the osmotic fragility of the patient's red cells to normal or to decrease the persistent reticulocytosis. The serum bilirubin fell from 2.1 to 1.0 mg. per 100 ml. on the first two days of treatment, but later rose to 1.7.

Case 3

The patient, a married woman aged 22, was known to have had anaemia in childhood and to have had four attacks of jaundice between the ages of 4 and 20 years. No evidence of a family history of haemolytic anaemia was obtained.

TABLE II.—*Haematological Observations in Case 3, Treated with A.C.T.H.*

Date	Hb (%)	R.B.C. (Mill./c.mm.)	W.B.C. (per c.mm.)	Retics. (%)	Eosinophils. Lowest Daily Count (per c.mm.)	Red Cell Osmotic Fragility: Strength of Saline in which Haemolysis Began	Serum Bilirubin mg./100 ml.	Treatment
7/12/50	80	3·81	8,200	5·8	150	0·6	3·2	
8/12/50				8·2	188	0·6	3·5	
9/12/50				9·4			3·1	
11/12/50	81	4·15	13,600	8·5		0·6		
12/12/50				8·1			3·4	
13/12/50				7·0			3·4	
14/12/50	81	4·10	12,400	11·2	175	0·6	3·8	25 mg. A.C.T.H. 6-hourly
15/12/50			8,600	7·6	125	0·6		25 ,, ,,
16/12/50			10,000	8·8	112	0·7	2·5	25 ,, ,,
17/12/50			9,900	7·2	92	0·7		25 ,, ,,
18/12/50	89		16,800	12·4	31	0·75	2·4	25 ,, ,,
19/12/50			13,600	13·6	87	0·75	2·9	25 ,, ,,
20/12/50	84	4·04	8,800	10·2	37	0·75	2·2	
21/12/50	88			9·8		0·75		
22/12/50	87	4·19		7·6	137	0·75	3·5	
23/12/50							2·9	
24/12/50						0·7	3·4	
25/12/50							3·1	
26/12/50	80	3·90	11,600	7·1	143	0·7		
27/12/50	85	4·12		6·8		0·7		
5/2/51	82	4·35	12,500	11·5				
6/2/51								Splenectomy
15/2/51	84	4·30	9,400	1·2			1·9	

On November 3, 1949, she was admitted to hospital on account of anaemia in the fifth month of pregnancy. Investigations at this time showed that she was suffering from haemolytic anaemia, the haemoglobin level being 75% and the reticulocyte count varying daily from 7% to 10%.

After giving birth to a healthy female child on April 8, 1950, the patient continued to suffer from haemolytic anaemia, and accordingly on December 6 she was re-admitted to hospital in order that A.C.T.H. therapy might be tried.

The patient felt well, but had slight clinical icterus. The spleen was enlarged 4½ in. (11.4 cm.) below the costal margin and the urine contained much urobilinogen. The marrow was hyperplastic and normoblastic. The blood figures were: haemoglobin, 80%; red cells, 3,810,000 per c.mm.; haematocrit, 29.5%; mean corpuscular volume, 77 μ^3; white cells, 8,200 per c.mm.; reticulocytes, 5.8%. Microspherocytes were present, and haemolysis began in 0.6% saline. Free acid was present in the gastric juice, and there was *x*-ray evidence of the presence of a gall-stone. The blood was Rh-positive, and, as on previous admissions, the direct Coombs test was negative. There was no evidence of "cold" or other abnormal agglutinins. The plasma proteins were normal and the Kahn test was negative.

It was decided to treat the patient with A.C.T.H., and 25 mg. was given six-hourly for six days, to a total dosage of 600 mg. The various findings before and after treatment are given in Table II.

The spleen became 2 in. (5 cm.) smaller at its tip within 24 hours of the beginning of treatment, and at the end of therapy it had become in all 3½ in. (8.9 cm.) smaller.

The effect of A.C.T.H. on the blood picture may be summarized as follows. There was no change in the haemoglobin or erythrocyte level. There was a fall in the eosinophil count and a rise in the total white cell count. The persistent reticulocytosis was not reduced nor was the osmotic fragility of the erythrocytes decreased, but there appeared to be a significant reduction of the serum bilirubin level from an average of 3.4 to 2.5 mg. per 100 ml. Within a few days of the cessation of treatment all figures had returned to the pre-treatment level. Accordingly, six weeks later splenectomy was successfully undertaken by Sir James Learmonth, and within a few days there was a fall in the reticulocyte count and serum bilirubin level.

Discussion

All the evidence in the first case would support the diagnosis of acquired haemolytic anaemia: the negative family history, the positive Coombs test, the transient effect of blood transfusions, and the presence of abnormal antibodies in the serum. With regard to the last-named, it would appear that two factors were involved: a powerful auto-agglutinin and an abnormal haemolysin. A somewhat similar case has been described by Dacie (1949). The administration of A.C.T.H. rapidly controlled the haemolytic process in Case 1.

A diagnosis of congenital haemolytic anaemia was made in Cases 2 and 3, despite the absence of a family history, because of the clear evidence of haemolytic episodes in childhood, the presence of increased fragility of the erythrocytes in hypotonic saline, the absence of circulating agglutinins or haemolysins, and negative Coombs tests. That the preparation of A.C.T.H. used was potent was indicated by the prompt fall in the eosinophil count, the rise in total white cell count, and the diminution in the size of the spleen in Case 3.

In contrast to Case 1 the only evidence in Cases 2 and 3 that the haemolytic process was temporarily affected was a moderate but significant fall in the serum bilirubin level in both cases. Whether larger doses of

A.C.T.H. or a longer course would have achieved any more striking results can be determined only by further clinical trials. All that can be said at the time of writing is that the effects of A.C.T.H. in the two cases of presumed congenital haemolytic anaemia were largely negative, in contrast to its dramatic effect in one case of acquired haemolytic anaemia.

In discussing the rationale for the use of A.C.T.H. in acquired haemolytic anaemia, Dameshek (1950) expresses the opinion that the beneficial effects may be due to a depression of antibody formation by the lymphoid tissue. Thorn (1950), on the other hand, feels that antibody formation may not be affected, but the reaction of the tissues to the antigen may be significantly altered. The fact that haemolysis was rapidly controlled in the first case while abnormal antibodies were still present does not support the view that the action of the adrenocortical steroids depends on a depression of antibody formation. An alternative hypothesis is that the damaging action of some product of the union of antigen and antibody is suppressed.

Summary

The results of the administration of A.C.T.H. in three cases of haemolytic anaemia are reported.

The administration of A.C.T.H. in a dose of 100 mg. daily for 10 days rapidly controlled the haemolytic phenomena in a case of acquired haemolytic anaemia, and symptoms have not recurred since.

In two cases of congenital haemolytic anaemia there was little or no response to the administration of A.C.T.H. in similar doses.

Evidence is brought forward to suggest that the control of haemolysis by A.C.T.H. in acquired haemolytic anaemia is not due to a suppression of the production of abnormal antibodies.

The A.C.T.H. used in these cases was supplied by the Medical Research Council, to whom we are indebted. We wish to express our gratitude to Dr. R. A. Cummings, Director of the Blood Transfusion Service, South-East Region, Scotland, who was responsible for the serological investigations.

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Speaking at Cardiff on March 12, the Minister of Health said the number of notifications of tuberculosis, which had been going up and down in the past 10 years, was now definitely showing signs of falling, and the number of deaths was going down. These developments were due to the applications of medical knowledge and skill supported by our National Health Service. In the years 1916–20 the average annual number of deaths from tuberculosis in England and Wales per million of the population had been 1,440; in 1940 it had been 670; in 1949 it had fallen to 450. Since the start of the National Health Service 3,550 additional hospital beds had been made available in England and Wales for the treatment of tuberculosis. He hoped that by the end of this year at least 2,000 more would be provided. Tuberculosis had for a long time been a more deadly enemy in Wales than in England. Mr. Clement Davies had pointed out in his report that, whereas in 1916–20 the mortality from tuberculosis had been the same in Wales as in England—namely, 1,440 per million of population—by 1936 the English figure had fallen to 680 and the Welsh only to 860. In 1949 the English figure was 415 and the Welsh 608.

EFFECT OF A.C.T.H. AND SUPRARENAL EXTRACT ON THE BONE MARROW*

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A connexion between the lymphoid tissues and the suprarenal cortex has been postulated with varying degrees of emphasis ever since Addison's (1855) classical monograph first appeared. Once Addison's disease had become recognized as a clinical entity, with its usually fatal termination, pathologists began to accumulate information about the lymphoid tissue hypertrophy which came to be regarded as one of the characteristic features of the disease, and which was even described as a "status lymphaticus" (Hedinger, 1907).

With the beginning of the modern study of the suprarenal cortex it became possible to investigate the action of individual hormones; and, of the two main groups of steroid hormones which the suprarenal cortex was known to produce, it soon became generally held that it was those with an oxygen atom at C 11 which were more especially associated with the lymphoid tissue changes. This view was challenged by Selye and his co-workers (Dontigny, 1946), but the demonstration (Hechter *et al.*, 1949), by perfusion of the isolated suprarenal with deoxycortone, that this substance could thereby be converted into 11-oxy compounds seemed to provide an obvious way of reconciling these conflicting points of view.

The most extensive work on the relation between the suprarenal cortex and lymphoid tissue is that of Dougherty and White (1945, 1947), who from 1943 to 1947 published a number of papers on the subject, and in 1947 summarized the results both of their own work and that of other investigators. Broadly speaking, their work followed two main lines. After the administration of adrenocorticotropic hormone and cortical hormones, they not only observed regressive changes in the lymphocytes and lymphoid tissue, but also attempted to correlate these with increased formation of gamma globulin and antibodies. The problem has been extensively reviewed elsewhere (Yoffey, 1950), and so far as antibody formation is concerned all that need be said here is that considerable doubt has been cast on either the increased production of antibodies in response to cortical hormones (Eisen *et al.*, 1947; Thatcher *et al.*, 1948) or the relationship between antibodies and lymphocytes (Fagraeus, 1948; Ehrlich *et al.*, 1949). It is doubtful, in fact, whether there is any correlation whatever between the lymphoid tissues and any of the plasma proteins (Andreasen *et al.*, 1948).

*Read by Professor Yoffey to the Section of Anatomy and Physiology at the Annual Meeting of the British Medical Association, Liverpool, 1950.

So far as the regressive changes in lymphoid tissue are concerned, four main lines of evidence have been adduced. The first line is an old observation by Downey and Weidenreich (1912), who described, in sections of lymph nodes, elongated processes of the lymphocyte cytoplasm which could then break off from the cell. This appearance we have been unable to confirm, nor, so far as we know, have other workers described it in sections, as originally noted by Downey and Weidenreich, even after the administration of A.C.T.H. and cortical hormones.

However, in smears of lymph nodes, Dougherty and White (1945) described lesser degrees of cytoplasmic budding, and they interpreted these as one way in which lymphocytes discharged gamma globulin into the blood. They also noted degenerative changes in the nuclei. One may, however, not infrequently find similarly damaged lymphocytes in "normal" lymphoid tissue, and what is therefore required is a quantitative comparison of the damaged cells in normal lymphoid tissue with those in the same tissue after the administration of A.C.T.H. or cortical extracts. Furthermore, it ought to be possible to devise a test to show increased fragility of the lymphocytes under such experimental conditions, but this we have not yet been able to do. It is pertinent to note in this connexion that A.C.T.H. and cortical hormones have no action on lymphocytes *in vitro* (Robertson, 1948; Delaunay *et al.*, 1949) Yoffey and Baxter (1946) actually observed hypertrophy of lymphoid tissue after daily injections of "eschatin" (an aqueous extract of suprarenal cortex) for one month. Their results, however, admit of several interpretations. Thus it is conceivable that the daily injections of eschatin induced a secondary atrophy of the animal's own suprarenals (cf. Ingle *et al.*, 1938), but that the eschatin was nevertheless much less potent in its action on lymphoid tissues than the secretion of the animal's suprarenals. It is not clear, also, to what extent general metabolic changes might react on lymphoid tissue.

The third line of evidence has been the observation of loss in weight of lymphoid tissue (including the thymus) after the administration of A.C.T.H., cortical extracts, or various steroid fractions. This type of change appears to be fairly well substantiated. The loss of weight might be due either to destruction of lymphocytes and inhibition of mitosis or else to their leaving the lymphoid tissues at a greater rate than usual. In the latter case they should enter the blood stream and give rise to a lymphocytosis.

This brings us to the fourth line of evidence—namely, that A.C.T.H. and cortical extracts may give rise to lymphopenia. Now lymphopenia is a phenomenon which can be observed clinically, and is therefore of immediate interest to the clinician. But, though readily observed, its significance may be very difficult to determine. Since the present work may have a direct bearing on this, a brief consideration of the factors which govern the level of the blood lymphocytes may not be out of place.

Level of the Blood Lymphocytes

Though we are still ignorant of the part played by the lymphocyte, its association with the lymphatic vessels provides an opportunity of forming some idea of the body's lymphocyte production. Lymphocytes are formed in lymphoid tissue, and then may enter the blood directly, as in the case of the spleen, or indirectly, by first obtaining access to the lymphatics, as in the case of the lymph nodes. Even in the lymph nodes, however, it is possible that a considerable number of lymphocytes enter the blood directly, by traversing the endothelium of the blood capillaries.

So far as direct entry of lymphocytes into the blood capillaries is concerned, we are no better off than with the other blood cells from the point of view of quantitative estimation. But in the case of the lymph-borne lymphocytes nature has provided a convenient bottleneck in the thoracic and right lymph ducts, where all the lymph of the body can be collected just as it is about to enter the blood stream, and its contained lymphocytes counted. This gives a *minimal* figure for the total lymphocyte output of the body. The figure is minimal not only because of the lymphocytes which are entering the blood directly, without the intermediation of the lymph stream, but also because of the possible existence of other lymphatico-venous communications.

Once the lymphocytes have entered the blood stream they do not remain there for very long. There is no satisfactory evidence of extensive destruction of lymphocytes in the blood, and, as large numbers of newly formed lymphocytes are continually entering the blood stream, one must assume that an equal number of these cells is steadily leaving, for otherwise the level of the blood lymphocytes would not remain constant. By comparing the figures for lymphocyte output with the number of lymphocytes normally present in the circulation, it is possible to draw up a rough balance sheet and estimate the turnover of the blood lymphocytes. Thus it has been calculated that in the dog the blood lymphocytes are replaced about twice daily (Yoffey, 1936), and in the cat and rabbit four or five times daily (Sanders *et al.*, 1940). It must be re-emphasized that this is a minimal replacement figure, for in all the quantitative studies only thoracic duct lymphocytes have been counted, and the right lymph duct ignored. Furthermore, there is no way of measuring the lymphocytes which directly enter the blood. If, as some workers have concluded—for example, Sanders *et al.* (1940)—the number of these latter lymphocytes is at all considerable, and if it equals in magnitude the lymph-borne lymphocytes, then in the case of the dog the lymphocytes would stay in the blood for something like six hours, and in the cat and rabbit for two and a half to three hours.

As to the destination of the many lymphocytes leaving the blood, three regions seem to merit the most serious consideration—namely, the lumen of the intestine, the connective tissues of the body, and the bone marrow. At one time excretion into the lumen of the alimentary canal (Bunting and Huston, 1921) was considered the most likely fate of the blood lymphocytes; but this view, though it still has its supporters, has on the whole fallen into disfavour. As to the bone marrow, while it has an astonishingly high lymphocyte content (see below), the presence of these cells has become involved in one of the most long-standing haematological controversies concerning the origin of the formed elements of the blood, and has tended to be more or less ignored.

Whatever the fate of the blood lymphocytes, it is clear that the number present in the blood is the result of a balance between those entering and those leaving it. With the notation of Drinker and Yoffey (1941), if x = the number of lymphocytes entering the blood over a given period and y = the number leaving it in that time, then normally $\frac{x}{y}=1$, and the level of the blood lymphocytes remains constant. If $x>y$ over a period,

then lymphocytosis will develop. This result will be obtained equally whether x be raised above or y depressed below the normal level. In other words, lymphocytosis may be of three types—namely, $\frac{x+}{y}$, $\frac{x}{y-}$ or $\frac{x+}{y-}$. Similarly there may be three varieties of lymphopenia—namely, $\frac{x-}{y}$, $\frac{x}{y+}$, or $\frac{x-}{y+}$. To which of these three types any lymphopenia belongs it is quite impossible to decide solely on the basis of blood counts. In the case of the lymphopenia produced by A.C.T.H. or cortical extract, the work of Dougherty and White (1947) would make one incline to the view that it was $\frac{x-}{y}$ in type—a diminished entry of lymphocytes into the blood stream. Direct measurement of thoracic duct lymphocytes has in fact appeared to confirm this interpretation (Reinhardt and Li, 1945; Yoffey, Reiss, and Baxter, 1946), but the experiments were not conclusive (see also Valentine *et al.*, 1948), for they were concerned only with thoracic duct lymphocyte output, and did not pay attention to the right lymph duct. Furthermore, they could not throw light on the numbers of lymphocytes directly entering the blood stream.

In view of all these facts, it was thought worth while to investigate the lymphocyte content of bone marrow after the administration of A.C.T.H. and cortical extracts. Attention was further attracted to the marrow because these substances produced changes in several other blood cells, giving rise to neutrophilia, eosinopenia, and perhaps even some degree of erythraemia (cf. also the occasional erythraemia of Cushing's syndrome). It seemed a not unreasonable working hypothesis that an effect on several different types of blood cells might be due to action on a single tissue—the bone marrow. Apart from these considerations, however, another reason for directing attention to the bone marrow was the fact that a technique had already been employed (Yoffey and Parnell, 1944) for making absolute counts of the nucleated cells of bone marrow. In view of the finding of Dougherty and White (1945), that after the administration of A.C.T.H. and cortical extracts there was destruction of marrow lymphocytes, it was thought that such a technique of quantitative analysis would demonstrate the change most convincingly

Material and Technique

The technique employed in the examination of the bone marrow is designed to give absolute counts of nucleated cells per unit of marrow volume. The principle of the method is to mix together known weights of bone marrow and oxalated plasma, and then shake up the marrow to obtain an even suspension of cells, which can be counted and from which smears can be prepared and stained in the usual way. The technique described previously (Yoffey and Parnell, 1944) has been improved upon by determining the specific gravity of both bone marrow and plasma, instead of assuming them both to be 1. Further, after many trials the marrow of the guinea-pig humerus was found to be the most suitable. It is far superior to the costal marrow of the rabbit, on which the previous counts were made, for it contains very little fibrous or fatty tissue and yields an admirable cell suspension

The marrow is obtained after the anaesthetized animal has been killed by bleeding in order to drain away from the marrow any excess blood. It is the admixture of marrow tissue with varying and unknown amounts of blood which renders the ordinary marrow biopsy so unsuitable for quantitative work. No doubt even with the present technique some blood was still retained in the marrow, the red cells in which ranged from 574,000 to 2,080,000 per c.mm., while those in the blood ranged from 4,330,000 to 7,000,000 per c.mm. Thus the method is still not perfect, and, depending upon the proportion of red cells which are mature marrow cells about to enter the blood to those which are blood cells contained in the vessels of the marrow, the counts obtainable will be somewhat below the true absolute count. In other words, the absolute figures for marrow lymphocytes are minimal.

From the cell suspension, counts were made with the haemocytometer in the usual way, and smears, with or without preliminary fixation in pure methyl alcohol, were stained with Wright's stain; the diluting fluid was at *p*H 6. For absolute counts it is of course necessary to include all cells, even those which are damaged. This was in any case no disadvantage, for special interest attached to changes in the number of damaged cells, which were fully expected to be increased. It will be seen from Table I that the number of these damaged cells is quite appreciable. It is to be noted, however, that both in the counting chamber and in wet preparations examined by phase contrast there was remarkably little evidence of cell damage in either the normal or the treated animals, and it was only in the dry smears that appreciable cell damage was observed. The tendency to cell damage, a recognized drawback of the dry-smear technique to be offset against its well-known merits, was regarded as a positive advantage in the present experiments, as it would presumably accentuate any trend towards increased fragility of the cells. It is worthy of note that, despite the cell trauma associated with the dry-smear technique, the figures obtained for mean lymphocyte percentage in normal marrow were of the same order as those found in guinea-pig marrow by Epstein and Tompkins (1943), both by supravital staining (11.3%) and in sections (10.2%).

The experiments fall into four groups. In the first group 25 normal marrows were counted. In Group II (nine experiments) marrow counts were made six hours after the intraperitoneal injection of 0.1 ml. of eschatin per 100 g. body weight, while in Group III marrow counts were made six hours after the injection of 1 mg. of pituitary A.C.T.H. (in 2 ml. of saline) per 100 g. of body weight. In Group IV 10 guinea-pigs were given intraperitoneal injections of saline (2 ml.) as controls; in five of these we used saline which had been in stock for some time, while in the other five pyrogen-free saline was employed.

TABLE I.—*Absolute Counts of Nucleated Cells per c.mm. of Guinea-pig Bone Marrow*

Type of Experiment	No. of Animals	Total Nucleated Cells	Total Myeloid Cells	Total Erythroid Cells	Damaged Cells	Lymphocytes	Monocytes	Reticulum Cells
Normal	25	1,235,000	404,800	153,000	457,000	144,800	54,800	7,200
Saline controls	10	1,500,000	520,000	239,000	451,000	183,000	76,800	8,000
Eschatin	9	1,151,000	363,400	105,900	379,000	269,000	38,500	2,400
A.C.T.H.	10	1,059,000	302,900	134,800	357,600	203,400	33,830	6,400

For supplies of eschatin we are indebted to the courtesy of Dr. J. Stanley White, of Messrs. Parke, Davis & Co., while the A.C.T.H. was kindly placed at our disposal by Dr. M. Reiss (cf. Reiss and Halkerston, 1950).

Results

Table II gives the mean results of the lymphocyte counts in the four series of experiments, expressed both as percentages and in absolute figures. The percentage of lymphocytes in the 25 normal marrows was 11.3 ± 1.4, and the absolute count $142,100 \pm 16,000$ per c.mm. of marrow. This corresponds quite closely with the counts obtained by Epstein and Tompkins (1943). Earlier counts on rabbit marrow (Yoffey and Parnell, 1944) gave the lymphocytes as 12–48% of the total nucleated cells of the marrow, and the mean absolute count as 61,000 per c.mm. Apart from the possibility of species differences, the present guinea-pig counts, for the reasons already mentioned, were technically much more satisfactory.

Substance Administered:	Eschatin	A.C.T.H.	Normal	Saline Controls
Number of Experiments:	9	10	25	10
Lymphocytes per cent of total nucleated cells of bone marrow	23.1 ±1·8	19·1 ±1·4	11·3 ±1·4	12·1 ±1·6
	t 4·63 p > 0·001	t 3·29 p < 0·01		t 0·347 p ≫ 0·1
Lymphocytes in absolute numbers per c.mm. of marrow	269,000 ±32,000	203,400 ±30,000	142,000 ±16,000	183,000 ±26,000
	t 3·55 p < 0·01	t 1·804 0·05 < p < 0·1		t 0·142 p ≫ 0·1

TABLE II.—Lymphocyte content of bone marrow in normal and experimental animals.

In the nine eschatin experiments the mean lymphocyte count was $269,000 \pm 32,000$ per c.mm. of marrow, and the percentage was 23.1 ± 1.8, while in the ten A.C.T.H. experiments the mean lymphocyte count was $203,400 \pm 30,000$, with a percentage of 19.1 ± 1.4.

The total absolute count of nucleated cells per c.mm. of marrow was $1,295,700 \pm 55,000$ in the normals, $1,151,000 \pm 105,000$ in the eschatin series, and $1,059,000 \pm 88,000$ in the A.C.T.H. series. The true absolute count is almost certainly somewhat higher, as already noted. Kindred (1942), working with paraffin sections of costal marrow in the rat, found an average count of 1,960,000 nucleated cells per c.mm. of marrow. In addition to differences in technique, however, there arises here also the question of species differences.

Discussion

The present data (average of 142,100 lymphocytes per c.mm. marrow) confirm the earlier findings of the high absolute count of lymphocytes in normal marrow. Since the average blood lymphocyte count in the series was 9,048 per c.mm., this is clearly not explicable as due to contamination with lymphocytes from the circulating blood. So far as the percentage of lymphocytes in human marrow is concerned, most clinical haematologists give a figure of the same order. Thus according to Whitby and Britton (1946) the lymphocytes form 5–20% of all the nucleated marrow cells. Very few absolute counts are available, but those reported in man (Lossen, 1910; Isaacs, 1937; Gordon, 1939) are of the same order as the present counts in the guinea-pig, which would suggest that there is also a similar absolute lymphocyte count in man.

Roughly, then, one in every ten of the nucleated cells of the adult bone marrow is a lymphocyte. This astonishingly high proportion of lymphocytes has, however, tended to be disregarded, for current haematological theory denies any genetic relationship between the lymphocytes and the erythrocytes and granulocytes. Thus, to quote one example of many, Piney and Hamilton-Paterson (1946) state that the lymphocytes constitute 14–21% of the marrow cells—that is, about one cell out of five—but then proceed to add that nevertheless "they are not part of the myeloid tissue proper." It certainly seems a little odd that one out of every five nucleated cells found in the marrow should have no real connexion with it.

Another factor which has made it somewhat easier to ignore the high lymphocyte content of the bone marrow has been the absence of quantitative data. To think of the lymphocytes as 10% of the nucleated cells of the marrow may not convey much. But if one translates this percentage into absolute figures, and considers the bone marrow as a whole, it becomes obvious that we are dealing here with one of the largest collections of lymphocytes in the body.

The high lymphocyte content of normal bone marrow is clearly something which calls for an explanation, and no satisfactory explanation has yet been forthcoming. The chief reason perhaps why the problem has not been more clearly envisaged is because it has become entangled with the numerous conflicting theories of blood formation. In general, clinical haematologists have tended to adopt a polyphyletic approach to the problem of haemopoiesis, according to which erythrocyte, granulocyte, and monocyte each arise from a specific stem cell; and the lymphocyte does not fit into this scheme of things. In consequence, its presence in the bone marrow has come to be regarded as a somewhat awkward phenomenon which is best ignored. But, irrespective of whatever theory of blood formation one accepts, the number of lymphocytes in the bone marrow ought to be an objective fact capable of being established quite independently.

Unfortunately the identity of the small lymphocyte has been the subject of controversy on so many occasions that almost any data appertaining to it have become suspect. An excellent instance is afforded by the bone marrow of the rat, in which the lymphocyte percentage has variously been estimated as 0.5% (Stasney and Higgins, 1935), 20% (Overbeck and Querido, 1938), 2.96% (Higgins and Macella, 1939), 21.7% (Aschkenasy, 1946), and $13.3 \pm 4.27\%$ (Endicott and Ott, 1945). Apart

from the question of true variation in the number of lymphocytes, the gap between the figures of the various workers seems to be due to difficulties of cell identification as much as anything else In the example just quoted (rat), Aschkenasy (1946) considers that the confusion is chiefly between the small lymphocyte and the early erythroblast. We have on occasion experienced this difficulty in the guinea-pig. Another source of trouble is the cell which Cunningham *et al.* (1925) termed the primitive cell, which at first they thought could be clearly differentiated from the small lymphocyte, though at a later date Sabin *et al.* (1936) seem to have come to the conclusion that this was not the case. Yet another source of confusion is with the cell which Rohr (1949) and others have termed the small reticulum cell.

While fully appreciating these difficulties in the identification of the small lymphocyte, we have endeavoured to overcome them in all cases by making in each animal suspensions of lymphocytes from a lymph gland, and examining these in stained smears before performing the differential count on the marrow. This, of course, still bases the identification of the small lymphocyte on morphological criteria alone, but, subject to that limitation, we believe that our data for marrow lymphocytes are reasonably accurate.

Effects of A.C.T.H. and Cortical Extract

There was no increase in the number of damaged cells after the administration of A.C.T.H. or eschatin. In fact, the percentage of damaged cells was slightly lower than the normal, though not significantly so, in both the A.C.T.H. and the eschatin series. This finding would appear to argue against changes, in either the lymphocytes or any other marrow cells, of the nature described by Dougherty and White (1945) in lymph nodes and thymus. It is no doubt conceivable that there may have been rapid and complete disintegration of the lymphocytes present in the marrow at the beginning of the experiment, and that there were no cell remnants to tell the tale. But if this were so, one would have to postulate either a rapid new formation of lymphocytes *in situ* from a non-lymphocytic precursor, or else the migration into the marrow from the blood of even greater numbers of lymphocytes than those which had been destroyed. In either case the response of the marrow lymphocytes would be radically different from that described by Dougherty and White in lymphocytes elsewhere.

In most of the experimental animals sections of cervical lymph nodes and thymus were examined, and no evidence was found of marked degenerative changes in individual cells, though in a number of instances the lymphoid masses appeared to be less densely packed than usual.

Instead, then, of the expected increase in damaged cells, the results indicate that one of the effects of A.C.T.H. or eschatin is to cause an increase in the marrow lymphocytes. This result was statistically significant in the eschatin experiments, and nearly so after A.C.T.H. Since there was nothing to indicate multiplication of the marrow lymphocytes *in situ*, the alternative explanation seems the more probable—namely, that there was an increased uptake by the marrow of lymphocytes from the blood. This might well be an important contributory, if not the main, factor in the development of lymphopenia after the administration of steroid hormones.

The increase in marrow lymphocytes just described occurred six hours after a single injection of A.C.T.H. or steroid hormones. What would be the effect of repeated injections? We have as yet no evidence to offer on this point, but it would seem reasonable to expect a steady growth in the lymphocyte population of the marrow. It is all the more interesting, therefore, to note that precisely the opposite effect may result. Thus Dameshek *et al.* (1950) obtained remissions in five cases of lymphatic leukaemia, with marked decrease in marrow lymphocytes, but "extraordinary rises in reticulocytes and platelets." They believe their findings to suggest "that a long-sought-for marrow stimulant may be at hand." It is to be noted that they concentrated their attention on the increase in the number of red cells rather than the decrease in the number of lymphocytes, presumably because they accepted the view that A.C.T.H. and steroid hormones caused lymphocyte dissolution, in which case the rapid disappearance of large numbers of lymphocytes presents no problem. But so far as bone marrow is concerned this does not appear to be the case, and it would seem that the rapid disappearance of marrow lymphocytes needs to be considered more carefully in relation to augmented erythropoiesis. In this connexion one may refer to the earlier findings of Dameshek and Valentine (1937) in pernicious anaemia, where before the beginning of liver therapy 27% of the myeloid cells were "typical lymphocytes having the characteristic size, shape, and staining reactions of the mature, or small, lymphocytes of the peripheral blood." Presumably, in the case of pernicious anaemia and liver therapy the question of lymphocyte dissolution does not arise: Dameshek and Valentine (1937) do not appear to have thought so. While there is not as yet enough evidence to warrant any definite conclusion, it seems clear that A.C.T.H. and the

Substance Administered:	A.C.T.H.	Normal	Eschatin	Saline Controls
Number of Experiments:	10	25	9	10
Damaged cells per cent of total nucleated cells of bone marrow	34·5 ±2·15	38·5 ±2·82	33·1 ±2·71	30·2 ±1·73
	t 0·855, p > 0·1		t 1·08, p > 0·1	t 1·77, 0·05 < 0 < 0·1
Damaged cells in absolute numbers per c.mm. of bone marrow	358,000 ±31,000	458,000 ±36,200	379,000 ±40,000	451,000 ±30,000
	t 1·67, p ~ 0·1		t 1·20, p > 0·1	t 0·11, p ≫ 0·5

TABLE III.—Damaged cells in bone marrow smears.

steroid hormones are likely to reawaken interest in the problems of haemopoiesis and the possible part played in them by the lymphocyte.

Summary

A quantitative technique has been employed to study the nucleated cells of the bone marrow, both in normal guinea-pigs and in guinea-pigs which were killed six hours after the administration of a single dose of A.C.T.H. or of cortical extract (eschatin).

In the normal guinea-pig red marrow was found to contain on the average 1,236,000 nucleated cells per c.mm., of which 144,800 were lymphocytes. The high lymphocyte content of bone marrow is not attributable to blood contamination.

There was no demonstrable increase of damaged cells in the marrow six hours after giving either A.C.T.H. or eschatin, but there was a statistically significant increase in the lymphocyte content after eschatin and an increase almost reaching the significant level in the case of A.C.T.H.

It is possible that increased uptake by the bone marrow of lymphocytes from the blood may be a contributory factor in the lymphopenia which may follow the administration of A.C.T.H. steroid hormones.

Whatever may be the effect of steroid hormones on lymphoid tissue in other parts of the body it has not been found possible by quantitative methods to demonstrate a destructive action on the lymphocytes of the bone marrow.

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SYMPATHECTOMY FOR HYPERTENSION

BY

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This paper presents a series of cases of severe essential and malignant hypertension which have been treated by thoraco-lumbar sympathectomy at Hammersmith Hospital since 1945, and which have been followed up in detail. A study of this material has given us some useful data on the early effects of sympathectomy for hypertension.

From November, 1945, to January, 1950, 35 carefully selected patients were operated upon. They were all in the care of the surgical unit under Mr. R. H Franklin. Most of the operations were performed by him, the remainder by his assistants.

These patients were referred to us for surgery by the Department of Medicine or sent from other hospitals, and before submitting them to operation extensive investigations were carried out to confirm their suitability for sympathectomy.

Routine for Investigation and Criteria of Operability

Apart from a thorough clinical examination, the routine investigation of all patients included electrocardiograms, *x*-ray screening of the heart and lungs, a study of the fundi, and the sodium amytal sedation test. An assessment of renal function was made by urine analysis, culture, and microscopy, specific gravity studies with concentration and dilution tests, blood-urea levels, urea-clearance tests, and intravenous pyelography.

With the aid of the information provided by the foregoing investigations, patients were selected for operation on the basis of the following criteria:

1. The patient must be under 55 and preferably under 50 years of age.

2. The diastolic blood pressure must be over 100 mm. Hg and the systolic level preferably over 200 mm. Hg.

3. There should be definite symptoms referable to hypertension, particularly severe headaches or disturbances of vision.

4. The patient must not be in cardiac failure.

5. Renal function must be adequate—that is, a blood-urea level of under 50 mg. per 100 ml. and a urea-clearance value of over 50% of normal. The intravenous pyelogram should not show any gross defect in outline or in rate of excretion.

6. If there has been a previous cerebral vascular accident the patient must have recovered from it without any serious residual disability.

7. The circulation should be labile—that is, capable of responding to rest in bed or to a sedation test by a fall in the diastolic B.P. level of at least 20 mm. Hg.

8. Malignant hypertension as demonstrated by the presence of papilloedema is a definite indication for surgery provided that the patient is not in the terminal stages of the disease with cardiac or renal failure.

Surgical Technique

In our first 14 patients the operation performed was the well-known extrapleural thoraco-lumbar sympathectomy of Smithwick (1940).

In May, 1948, we altered our technique to one of transpleural thoracotomy and sympathectomy, as it was noticed that during thoracotomies for other conditions an excellent view of a considerable extent of the thoracic sympathetic chain and its branches could be obtained, and, in addition, open thoracotomy permitted a thorough re-expansion of the lung under direct vision at the end of operation.

This approach has remained in use up to the present and has been carried out 41 times on 21 of our patients.

Details of the Operation

General anaesthesia with thiopentone, cyclopropane, oxygen, and curare, respiration being controlled through a cuffed endotracheal tube, is used. The patient is placed in the lateral position with the side to be operated on uppermost. A wedge is placed under the lower ribs, and the arms are drawn forwards away from the chest on supports. An incision approximately 10 in. (25 cm.) long is made in the line of the eighth rib and is carried down to the rib. Bleeding points are coagulated with diathermy. A segment of the eighth rib between the angle and the costochondral junction is resected subperiosteally. At this stage the intercostal nerve at the lower edge of the rib bed is found and a few inches of it close to the angle of the rib is excised. We believe that this procedure reduces the incidence of post-operative pain.

The pleura is next opened along the bed of the rib and the lung is permitted to collapse. Rib spreaders are inserted and the lung and diaphragm retracted by an assistant. The great splanchnic nerve is the most easily visible branch of the thoracic sympathetic trunk, and can be clearly seen through the pleura overlying the sides of the vertebral bodies near the diaphragm. The pleura is incised at this place and the great splanchnic nerve is picked up and followed cranially to its highest origin from the sympathetic trunk at the level of the sixth (or sometimes the fifth) thoracic ganglion. The ganglionated chain is then traced downwards to the diaphragm by incising the pleura over it. The diaphragm is now elevated by blunt finger or gauze dissection from the posterior abdominal wall at the point where the chain passes under it and an illuminated retractor is inserted into the space so made (deep to the medial lumbo-costal arch) and the upper lumbar chain is exposed. In this way the first lumbar ganglion (where this is present) is brought into view, and with suitable retraction it is sometimes possible to see the second lumbar ganglion. Only very rarely is it possible to see the lumbar chain caudal to this by simple retraction.

The chain over an extent from the sixth thoracic ganglion to the first lumbar ganglion inclusive, together with the splanchnic nerves, is thus exposed and is resected (see Fig. 1). This resection is performed between Cushing's silver clips in order to control any small vessels which run with the nerves and so that the clips could act as markers in post-operative *x*-ray films to confirm the extent of removal of the sympathetic chain. Where there is a strong clinical suspicion of the presence of an adrenal tumour (phaeochromocytoma) and it is considered necessary to explore that organ, the diaphragmatic origin is divided with scissors and a satisfactory approach obtained.

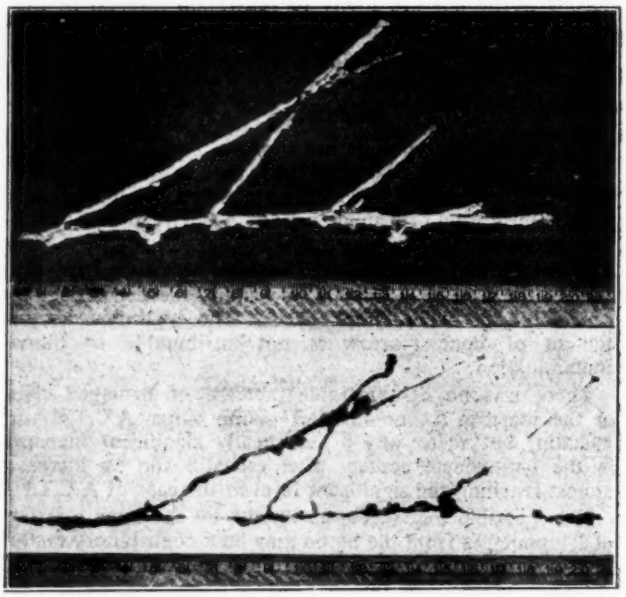

FIG. 1.—Typical specimens of the sympathetic ganglionated chain with the splanchnic nerves as removed in the transpleural operation.

The lung is next reinflated by the anaesthetist and any segment which remains collapsed in spite of positive endotracheal pressure may be expanded by massaging air into it from a neighbouring segment until the lung is completely aerated.

The chest is now closed in layers with catgut without drainage, but in those cases in which there is a tendency to ooze within the pleura an intercostal catheter is inserted into the chest through a separate stab incision and drained into an underwater seal for 48 hours.

The opposite side is similarly treated two to three weeks later.

Material

Between November, 1945, and January, 1950, 35 patients were operated on (23 women, 12 men). The youngest patient was aged 20 and the oldest 53. The average age at operation was 41.5 years. Of the 35 patients, 24 had essential hypertension and 11 had malignant hypertension as shown by the presence of papilloedema.

Sixty-eight operations were performed; in two patients only one side of the operation was completed. Twenty-seven operations were of the extrapleural Smithwick type and 41 were of the transpleural variety. We have maintained contact with 33 of these patients, mostly by their regular attendance at the follow-up clinic. A few patients living too far from London for routine attendance have been followed by corresponding with them and with their family doctors. Two patients are untraced. These 33 patients have been followed up for

a period varying from 2 to 51 months from operation—the average period of follow-up has been 18.5 months in those with essential hypertension and 18 months in those with malignant hypertension.

The results of sympathectomy for hypertension in these patients are considered under the following headings: (*a*) the effects on the blood-pressure levels; (*b*) the relief of symptoms; (*c*) the production of adverse symptoms; and (*d*) morbidity and mortality of the operation.

Effects on the Blood-pressure Levels

Certain standards of recording B.P. levels have been adopted, and these together with some definitions are quoted to make the use of subsequent terms clear.

All B.P. levels have been taken with the patient recumbent after a period of rest of at least five minutes. The B.P. level "before operation" represents the figure recorded on the day of admission to hospital. The B.P. "after operation" is the level recorded just before the patient's discharge from hospital, and the B.P. "at present" is the level measured at the out-patient clinic on the visit closest to January 1, 1950.

In order to reduce the mass of recordings to a more easily appreciated form, an arbitrary scale of classification has been chosen. It is generally agreed that in hypertension the diastolic B.P. level is a more reliable measure of the severity of the disease than the systolic B.P. Furthermore, since diastolic levels are less liable to the gross fluctuations which are observed in the systolic levels in response to emotion or exertion, our results have been classified on the basis of change in the diastolic levels. A fall in the diastolic level of 20 mm. Hg or more is considered to represent a "significant" improvement, a fall of 19 mm. Hg or less represents "no change," and where the diastolic level has in fact risen after operation the change is recorded as "worse."

In the 24 cases of essential hypertension that have been treated the effect of sympathectomy on the diastolic levels "after operation" was to produce a "significant" fall in 17 cases and "no change" in six cases. One patient died during the second stage of the operation (see Table I). The levels recorded "at present" after

TABLE I.—*Blood Pressure Changes After Sympathectomy*

No. of Cases Completing Operation	B.P. Changes "After Operation"		B.P. Changes "At Present"	
Essential hypertension (24)	Significant fall	17	Significant fall	6
	No change	6	No change	13
	Died during operation	1	Worse	1
			Died	3
			Untraced	1
Malignant hypertension (9)	Significant fall	7	Significant fall	2
	No change	2	No change	4
			Died	2
			Untraced	1

an average follow-up period of 18.5 months show that only six patients have maintained a "significant" improvement in B.P., 13 show "no change," one is worse, three are dead of the disease, and one is untraced.

Thus we see that only 6 out of 24 of our patients (25%) have so far maintained a "significant" fall in the B.P. level since operation.

Eleven patients with malignant hypertension were operated on, but in two of them only one side of the operation was completed: one because of fulminating progress of the disease after the first stage, terminating in death three months later; the other, who was discharged from hospital between stages, failed to return for the second operation, and died 34 months later of the effects of the disease. Of the nine patients in whom both sides of the operation were completed, seven had a "significant" fall in B.P. "after operation" and two had "no change" "At present," after an average follow-up period of 18 months, only two patients have maintained a "significant" fall in B.P.; four show "no change," two died from the disease, and one is untraced (see Table I).

Thus we see that six out of nine patients are alive after an average of 18 months and only two of these have maintained a significant improvement in blood pressure.

Relief of Symptoms

With respect to the relief of symptoms our patients have fared considerably better. Before sympathectomy all had symptoms due to hypertension. The commonest was headache, often of a severe and incapacitating nature. Another frequent complaint was disturbance of vision sometimes approaching complete blindness. Other symptoms included breathlessness, tiredness, inability to concentrate, epistaxis, angina of effort, and those symptoms associated with cerebral vascular accidents.

Amongst 24 patients with essential hypertension, 23 have been followed up to "the present." Of these, 16 are virtually symptom-free and at full work, two have had partial relief, two are unaffected symptomatically, and three are dead (Table II).

TABLE II.—*Symptomatic Relief Following Sympathectomy*

No. of Cases Completing Operation	Symptomatic Changes "At Present"	
Essential hypertension (24)	Symptom-free	16
	Partial relief	2
	No change	2
	Died	3
	Untraced	1
Malignant hypertension (9)	Symptom-free	4
	Partial relief	2
	Died	2
	Untraced	1

Of nine patients with malignant hypertension who underwent both sides of the operation, four are virtually symptom-free "at present" and at work, two have obtained only partial symptomatic relief and are semi-invalids, two are dead of the disease, and one is untraced (Table II).

Production of Adverse Symptoms

Side-effects associated with bilateral thoraco-lumbar sympathectomy in our patients have been common enough to merit detailed consideration.

1. *Pain and Hyperaesthesia.*—A neuralgic pain or a zone of hyperaesthesia radiating along the side of the chest to the epigastrium referred to thoracic segment 8 (or 9) has developed in 11 of the 35 patients. This effect has appeared within the first few weeks after operation, and has in all cases disappeared after a few months. The pain has been of varying intensity, sometimes minor but sometimes of enough severity to require attempts at intercostal nerve block for its relief. We believe that since the practice of deliberately excising a portion of intercostal nerve at operation was introduced the incidence and severity of this effect have been reduced. Generally the pain or hyperaesthesia is well tolerated, and the patients will endure it without distress provided they are reassured of its benign nature and early disappearance.

2. *Post-operative Compensatory Sympathetic Effects.*—It is now well recognized that after major excisions of the

sympathetic nervous system the residual portion becomes hypersensitive to the stimuli which normally activate it. In this respect, six of our patients have developed vasospastic manifestations of a subjectively noticeable degree. This effect has appeared in varying grades of severity, the least severe being an increased sensitivity to cold. Intermediate grades have appeared with the sensation of "pins and needles" in the toes and fingers, and the most severe with attacks of pallor in the fingers resembling a form of Raynaud's phenomenon but arising spontaneously and not necessarily in response to cold or to emotion.

All these effects have been temporary and not incapacitating. One of our patients, an Anglo-Indian lady, developed a temporary hyperhidrosis of the palms and fingers which subsided in the course of a few weeks.

Only four of our patients developed post-operative postural hypotension, with a feeling of faintness on rising after a period of recumbency. Again this has not persisted for more than a few months.

Morbidity and Mortality of the Operation

In operating close to or within the pleural cavity we have found it common for our patients to develop minor post-operative chest complications, usually of the nature of small effusions of clear or blood-stained fluid or very small collections of air. These minor complications have for the most part resolved spontaneously or following one or more aspirations of the chest.

Chest complications of a more serious nature that have occurred in five patients are listed separately in Table III. Major complications outside the chest

TABLE III.—*Post-operative Chest Complications*

Nature of Complication	No. of Cases	Type of Sympathectomy	Treatment of Complication and Result
Haemothorax ..	1	Transpleural	Open evacuation of clot and resuture of chest. Cured
Atelectasis of lung	1	,,	Bronchoscopic aspiration of mucus and breathing exercises. Cured
Valvular tension pneumothorax	1	Smithwick	Continuous pleural aspiration. Cured
Chylous pleural effusion	1	Transpleural	Repeated aspiration of chest. Cured
Empyaema thoracis	1	,,	Decortication after sterilization of pus with streptomycin. Cured

occurred in three patients: one developed a haemoperitoneum from spontaneous rupture of the vessels at the splenic hilum during convalescence, which was cured by ligation and splenectomy; one developed a deep phlebothrombosis of the calf veins, which resolved under heparin; and one female patient, 18 weeks pregnant, miscarried after a Smithwick operation for malignant hypertension.

In 68 operations we have only had one fatality—an operative mortality of approximately 1.5%. This compares favourably with Smithwick's (1948) series, which had an operative mortality of 2.2%.

We have not had a death so far from the transpleural sympathectomy. Our single operative death occurred during the second stage of a Smithwick sympathectomy in February, 1947. The patient was a diabetic woman aged 49 with severe essential hypertension who suffered a considerable fall in blood pressure immediately after the division of the sympathetic chain; in spite of all attempts at resuscitation she died on the table of acute peripheral circulatory failure. Nowadays, the patient would probably have survived this crisis with the use of methylamphetamine hydrochloride *B.P.C.*, a drug which we have since found to be a vasopressor agent of great value in controlling hypotension during and after operation.

Post-operative Tests of Sympathetic Denervation

In 12 patients I carried out a series of dye sweating tests at various stages in an attempt to correlate the extent of denervation with the area of loss of reflex sweating.

In those patients in whom the denervation extended from the ganglia T 6 to L 1 inclusive, photographic sudograms were obtained showing zones of absent sweating over the spinal dermatomes T 6 to T 11 plus variable patchy extensions into dermatomes T 12 and L 1 (see Fig. 2).

FIG. 2.

FIG. 3.

FIG. 2.—Photograph showing the zones of absent reflex sweating (unstained) after resection of the sympathetic chain from ganglia to T 4 to L 1 inclusive on the right side and T 6 to L 1 inclusive on the left side. The lower boundaries are patchy, and sweating still persists in the "bathing-trunk" area, indicating residual sudomotor activity in this zone.

FIG. 3.—Sudogram in a patient following resection of the sympathetic chain down to and including ganglion L 2 on the right side and L 1 on the left side. The right lower limb is "dry" except for a wide zone of residual sweating on the front of the thigh. The left lower limb sweats except for a patch on the upper thigh.

When the level of section of the chain was below the ganglion of L 2 sweating in the shin and foot was almost completely lost; it was retained to a variable degree in the thigh, and completely retained in the groin folds and in the pubic and medial crural areas (dermatomes T 12; L 1, and L 2) (see Figs. 3 and 4).

This finding is in agreement with those of Ray and Console (1948), and confirms the presence of residual sudomotor pathways to dermatomes T 12, L 1, and L 2 after resection of the ganglia T 12, L 1, and L 2. This is probably explained, as suggested by Boyd and Monro (1949), by the presence of "intermediate" ganglia carrying sudomotor fibres situated outside the main sympathetic trunk which therefore remained behind after sympathectomy.

Discussion

We now operate as a routine by the transpleural route because of the simplicity and ease of approach to the lower thoracic chain and its branches. This

FIG. 4.—Sudogram of another patient following a resection; the lower limits are identical with those in the patient shown in Fig. 3. The overall picture of absent sweating is similar to that in Fig. 3, but the zone of residual sweating in dermatomes T 12, L 1, and L 2 is considerably less.

route has the disadvantage of not often permitting a view of the lumbar chain below the first lumbar ganglion; but this we believe is only a minor disadvantage, as there is no conclusive evidence that the additional removal of ganglia L 2 and L 3 significantly improves the results. We are therefore content to section the lumbar chain as low as our approach permits — that is, usually just below the ganglion of L 1.

Smithwick (1950) states: "It is my belief that a thorough denervation of the splanchnic bed, such as is obtained by removing the sympathetic trunks bilaterally from the eighth thoracic to the first lumbar ganglion inclusive, together with the splanchnic nerves, is the procedure of choice for most cases." This can be very readily achieved by the transpleural route.

In order to obtain a statistically significant evaluation of the results of sympathectomy for hypertension it is necessary to follow a large classified series of cases treated by surgery for at least 10 years and to compare it with a similar series treated medically. Nevertheless the results of the follow-up of this small series is of value, for even at this early stage an appreciation of the value of the operation has been obtained and the trend of the results is becoming apparent.

With regard to severe essential hypertension the early post-operative fall in B.P. was satisfactory in 17 out of 24 cases, but only 6 cases maintained this improvement after an average of 18 months. If we consider these results of the B.P. changes alone, a pessimistic view of the operation could be taken, but it is also necessary to allow for the symptomatic relief which the operation has achieved for our patients.

At present 16 of the original 24 patients (66.6%) are virtually symptom-free and have returned to normal work. This in my opinion represents a result of considerable value. Furthermore, the gratitude which has so often been expressed by individual patients for the relief of distressing symptoms has convinced us that the operation is worth while in spite of the failure in many cases to achieve any satisfactory fall in B.P. There is also evidence (Smithwick, 1948) that sympathectomy persistently reduces or even abolishes those rises of blood pressure which are normally caused by reflex vasoconstriction, and it is likely that this mechanism protects the circulation against dangerous physiological elevations of pressure and can be regarded as a favourable effect of operation even in those cases in which the B.P. levels have not fallen significantly after sympathectomy.

In the nine patients with malignant hypertension who have completed both sides of the operation and have been followed for an average period of 18 months, six are known to be alive, and four of these are virtually symptom-free and at work.

As approximately 80% of patients with malignant hypertension die in the first 12 months of the disease in spite of medical treatment (Keith, Wagener, and Barker, 1939), these results indicate a definite benefit following surgery.

On theoretical grounds it would seem logical to operate on the mildest cases of essential hypertension in the hope of halting the progress of the disease, but we have refrained from doing this, since these are just the cases in which there is relatively a better prognosis without surgery and in which it is difficult to judge the outlook in the individual case. Furthermore, in the absence of symptoms, it is probably unjustifiable to operate for mild hypertension and submit the patient to the hazards of morbidity and mortality.

Conclusions

So far, a closer study of the more successful of the results of our treatment of essential hypertension reveals that they occurred most often in women who had developed a severe hypertension after a pregnancy complicated by toxaemia or eclampsia.

In malignant hypertension our best results to date have been obtained in patients operated on in the early stages of the disease, before the heart and kidneys were seriously impaired.

A survey of those cases which derived least benefit from sympathectomy reveals that they were mostly in the older age groups, particularly over 49, or had suffered from borderline or established cardiac failure before operation. One patient with essential hypertension due to an undetected chronic pyelonephritis was submitted to sympathectomy, but after a period of six months' relief the hypertension entered the malignant phase and she died in uraemia 40 months after operation. Chronic pyelonephritis should be carefully sought for before operation, since it may be possible to remove a kidney for unilateral disease, to the benefit of the patient.

The list of criteria of operability given earlier in this paper summarizes our present views on this matter, although fulfilment of these criteria does not guarantee that the patient will benefit from sympathectomy.

It should be remembered that sympathectomy for patients with severe hypertension is a palliative measure and that in the long run these patients will die of the effects of hypertension. Sympathectomy can, however, be applied with benefit to a group of carefully selected patients, and as it makes life more tolerable for most of them, and seems to prolong the useful duration of life in some, particularly the malignant cases, it appears at this interim stage to be a procedure of value.

Summary

This paper presents an interim survey of 35 cases of severe essential and malignant hypertension which have been treated by thoraco-lumbar sympathectomy at Hammersmith Hospital since 1945.

The criteria of selection for operation are summarized, and the technique of the transpleural sympathectomy is described in detail.

After a follow-up period varying from 2 to 51 months (average 18 months) the survey reveals that so far only 25% of the patients have maintained a significant fall in

blood pressure, but that 66% of them have been relieved of incapacitating symptoms and have returned to work.

The prognosis for malignant hypertension so far shows a definite improvement as a result of sympathectomy.

For a limited but definite group of patients with hypertension, sympathectomy is a valuable procedure.

I wish to thank Mr. R. H. Franklin for permission to publish his cases and for his valuable advice in the preparation of this paper.

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THE EFFECT OF A.C.T.H., CORTISONE, AND D.C.A. WITH ASCORBIC ACID ON "FORMALIN-ARTHRITIS"

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In 1949 Selye produced an arthritis in rats by injecting formaldehyde solutions into the feet. He said that adrenocorticotropic hormone (A.C.T.H.) and "cortisone" prevented the acute and chronic stages of "formalin-arthritis," having an action opposite to that of deoxycortone acetate (D.C.A.), which exacerbated the condition. He further asserted that the lesions of "formalin-arthritis" resembled, microscopically, in the acute oedematous stage the rheumatic, and in the chronic stage the rheumatoid, type of arthritis.

In clinical treatment Lewin and Wassén (1949) and later among other workers, Le Vay and Loxton (1949) reported that the treatment with D.C.A. and ascorbic acid parenterally was effective in cases of rheumatoid arthritis. This has been disputed by many workers (Empire Rheumatism Council, 1950).

Below we report our experience with "formalin-arthritis"; the histological picture of this condition will be presented elsewhere (Bourne, 1951; Bourne, Parkes, and Wrigley, 1951).

At an early stage in the work it was recognized that means should be sought for estimating quantitatively the changes in limb volume which occurred. Selye gave no indication that more than visual observation was employed; and indeed his illustrations would support the impression that the differences to be observed were sufficient for subjective evaluation to be adequate. Brownlee (1950), however, followed the changes in limb volume in the course of development of "formalin-arthritis" in rats by calliper measurements. The method we used (Bergel, Parkes, and Wrigley, 1951) consists in photographing a limb in such a way as to obtain a negative silhouette, which is cut out and weighed. Twelve such shapes provide enough paper for reasonable accuracy in weighing. Duplicate exposures are made of front and side aspects of the limb in groups of six rats, and the silhouettes are bisected into regions corresponding respectively to "foot" and "ankle," which are the parts affected by the acute and chronic stages of "formalin-arthritis." The product of the weights of corresponding front and side shapes serves as an index of limb volume for the group.

It was considered of importance that work should be accompanied by some knowledge of the histological changes attending the course of "formalin-arthritis." Consequently, a series of rats were injected with formalin (see below) and killed after the elapse of a period varying from five minutes to four weeks. Limb volumes were measured before injection and immediately before sacrifice. Ankle-joints and adrenals were sectioned, the histological details of which are reported in another paper (Bourne, 1951). They show that with increase in the period following injection there is a progressive increase in the degree of inflammatory reaction of the ankle-joint of the injected limb, which is followed to a smaller degree by changes in the joint of the contralateral limb. At the same time there is a progressive decrease in lipoid content of the adrenal cortex. These changes can be correlated with the alteration in swelling of the injected foot and ankle. However, while there appears to be a return of the histological appearance of the contralateral ankle-joint to normal, the degree of inflammation of the joint of the injected limb increases still further. By the end of the fourth week after injection all limb volumes have returned to normal.

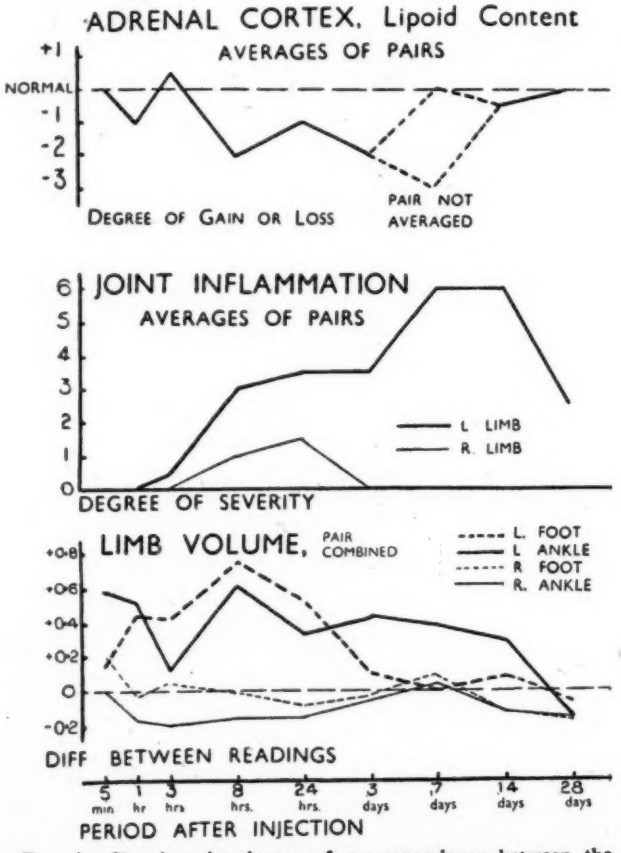

FIG. 1.—Showing the degree of correspondence between the course of the lesion histologically and the changes in limb volume.

Corresponding to this, the joint histology shows a return towards normality, whilst the adrenal lipoid content is normal.

The arbitrary assessment of histological severity of the lesions has been plotted against a non-scalar disposition of the periods between injection and sacrifice to form Fig. 1. This shows the degree of correspondence between the course of the lesion histologically and the changes in limb volume.

Effects of Treatment upon "Formalin-arthritis"

Except where otherwise stated, "formalin-arthritis" was induced in male rats of the order of 150 g. weight, distributed in balanced groups, by the regular injection of 0.1 ml. of 2% formaldehyde beneath the plantar surface of the left hind paw, on two occasions separated by an interval of five days, starting on the second or third day of the experiment. Wistar rats were used, obtained from the Agricultural Research Council, and maintained throughout on rat cubes made to the specifications of the Medical Research Council.

D.C.A. and Ascorbic Acid

Experiment 1

Three groups of six rats were injected with formalin on the third and the eighth day of the experiment. Two of these groups were treated as follows. Group A: Intramuscular injections of 0.25 mg. D.C.A. in saline suspension twice daily, starting on the second day of the experiment. Group B: Injections of D.C.A. as in

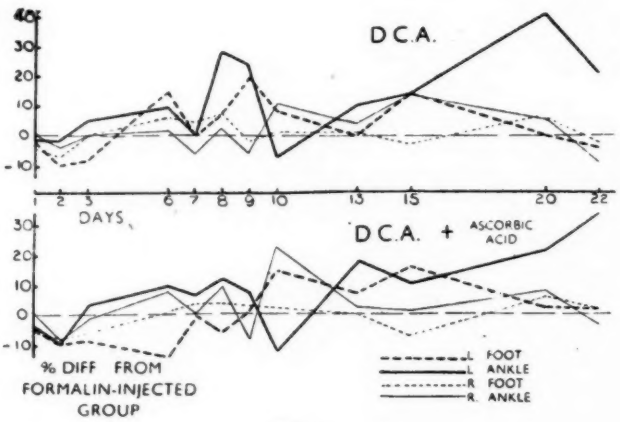

FIG. 2.

Group A, together with an intramuscular injection of 25 mg. ascorbic acid in neutral solution twice daily, also starting on the second day.

Measurements were begun the day previous to these injections in order to obtain an estimate of normal limb volumes. Since, in the beginning of this experiment, silhouettes were estimated by planimetry and only later by the weighing method described, the values plotted in Fig. 2 are calculated from the original measurements.

The results show that, over the three weeks of the experiment, volumes of the injected limb tend to be greater in both treated groups than in the untreated group. This, we conclude, is due to D.C.A., the action of which is not modified by ascorbic acid. Histological examination of the joints confirms the absence of a significant difference between the two treated groups, in both of which the adrenal cortex showed severe loss of lipoid.

Experiment 2

Two groups of six rats were injected with formalin a third group serving as control. Of the two injected groups, one was treated with intramuscular injections of 0.5 mg. D.C.A. in 0.1 ml. of arachis oil and 25 mg. ascorbic acid in 0.4 ml. neutral aqueous solution, mixed in one syringe and given twice daily. This mode of injection was based on that claimed to be a successful modification of the treatment of Lewin and Wassén

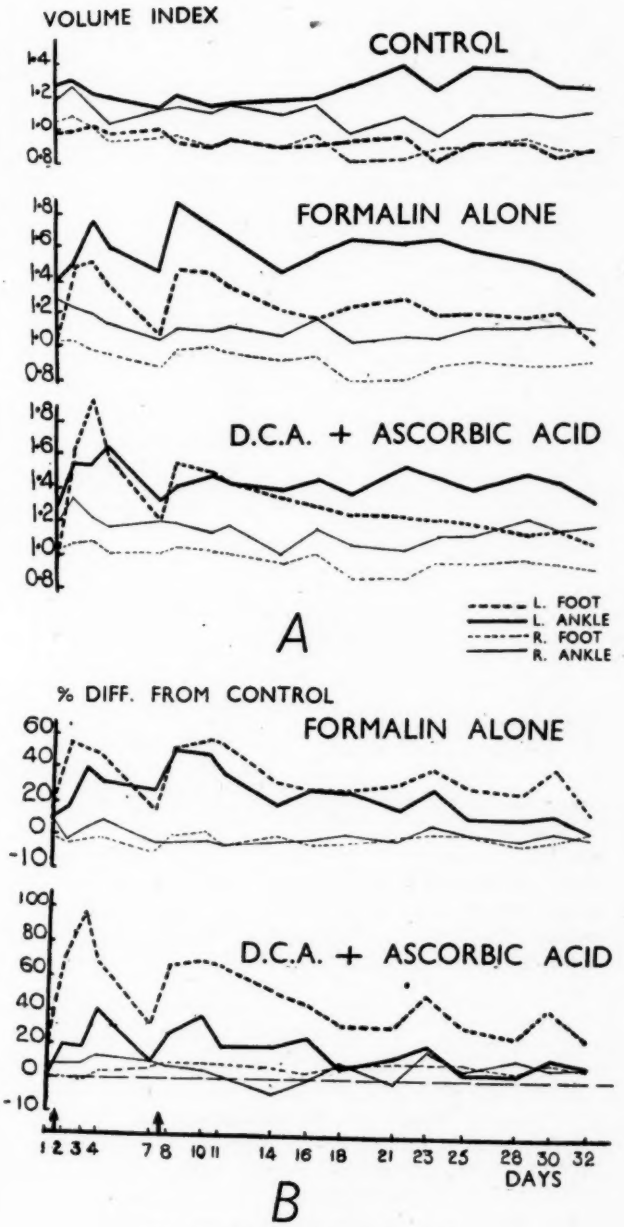

FIG. 3.—Results of Experiment 2.

(1949) by Le Vay and Loxton (1950). Treatment was continued for four weeks, and measurements for the three groups are given in Fig. 3,A.

Fig. 3 shows that measurements for the control group fluctuate with time about fixed levels, as do those for the uninjected limbs of the other groups. This is presumably due mainly to factors in measurement (Bergel, Parkes, and Wrigley, 1951). Fig. 3,A indicates a tendency for the injected foot in the group treated with

D.C.A. and ascorbic acid to be larger than that in the untreated group, particularly in the earlier stage of the experiment, while the reverse is true for the corresponding ankle, indicating protection. Subsequent histological examination, however, showed clearly that the condition of the treated group remained worse than that of the untreated group.

A.C.T.H.

Experiment 3

Four groups of six rats were used—one control and three injected with formalin. Two of the injected groups were treated by intramuscular injection of 0.1 mg. A.C.T.H. and 0.25 mg. A.C.T.H. respectively, twice daily for eight days out of a period of ten, starting on the day before the first formalin injection. The measurements over this period are plotted in Fig. 4,A.

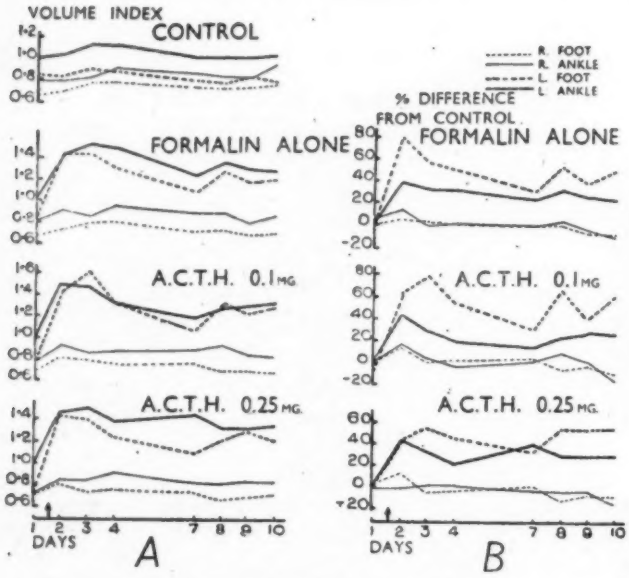

FIG. 4.—Results of Experiment 3.

The results show that no obvious effects were produced by either dose of A.C.T.H., which is also borne out by the results of histological examination of joints from animals sacrificed at the end of the experiment.

Experiment 4

The inactivity of the two dose levels used in the last experiment could be attributed to the fact that they were chosen before we were apprised of the true potency of the sample (about 190% Armour standard La 1a). Three further groups of six rats were therefore taken, and, of the two groups injected with formalin, one was given intramuscular injections of 1 mg. A.C.T.H. twice daily. The results are given in Fig. 5,A. They show a tendency for the joint of the injected limb to be smaller in the group receiving A.C.T.H. than in the untreated group, while the reverse is true of the injected foot, particularly following the second injection of formalin. Histological examination showed little difference between treated and untreated groups except that the adrenal cortex in the former appeared to have more than the normal content of lipoid A further dose level of A.C.T.H. was tested (see Experiment 6).

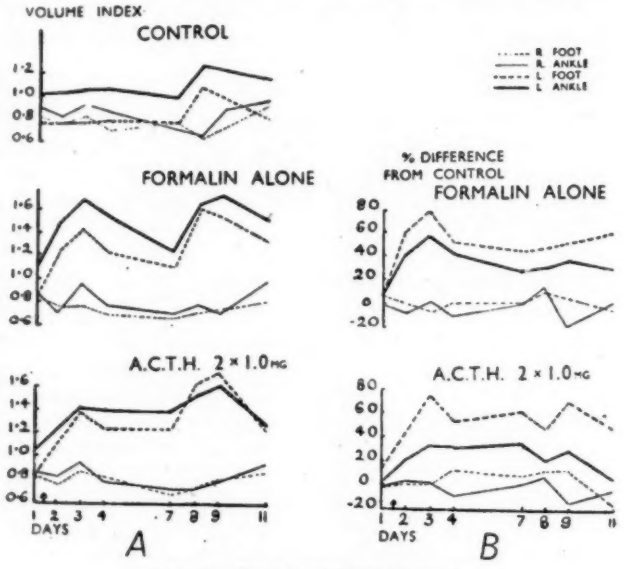

FIG. 5.—Results of Experiment 4.

Cortisone

The cortisone available was sufficient for two experiments lasting four days, using 2.5 mg. twice daily. Thus the only action which could be sought was upon the acute effects of a single injection of formalin. The cortisone was injected subcutaneously, and treatment was begun the day before the formalin injection. In all these points the procedure of cortisone administration agrees with that described by Selye (1949) Although he adrenalectomized his animals, it was decided not to do so, since we felt that the cortisone action should be demonstrable without it.

Experiment 5

Results presented in Fig. 6,A show that cortisone exerted no protective effect whatever. The histological picture at the end of the experiment closely resembled that described for the group treated with A.C.T.H. in Experiment 4.

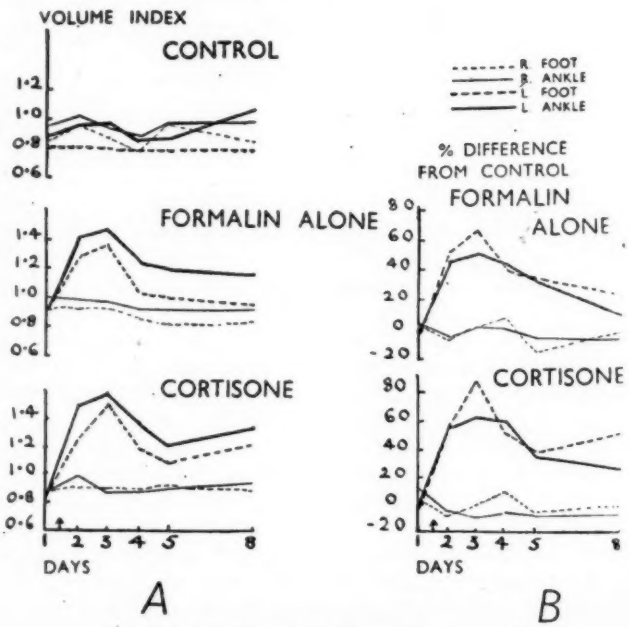

FIG. 6.—Results of Experiment 5.

Experiment 6

Experiment 5 was repeated, and in addition a fourth group of six rats received subcutaneous injections of 1 mg. A.C.T.H. five times daily, at intervals of two hours, for eight days.

The results of this experiment are presented in Fig. 7,A. They show that, judged by ankle volume, the response to formalin was somewhat less than in former experiments, although both cortisone and A.C.T.H. appeared to cause a reduction even beyond this in the degree of swelling produced. In the case of A.C.T.H. the ankle volumes barely exceeded those of the control group. However, the general condition of the animals in these two groups deteriorated and loss of weight occurred. This aroused the suspicion that the protection afforded to the formalin-injected limb was spurious, the effect on limb volume merely reflecting general emaciation. This was confirmed by the observation that the volumes of the uninjected limb in these groups fell below those in the other two groups in a manner corresponding to the loss in weight.

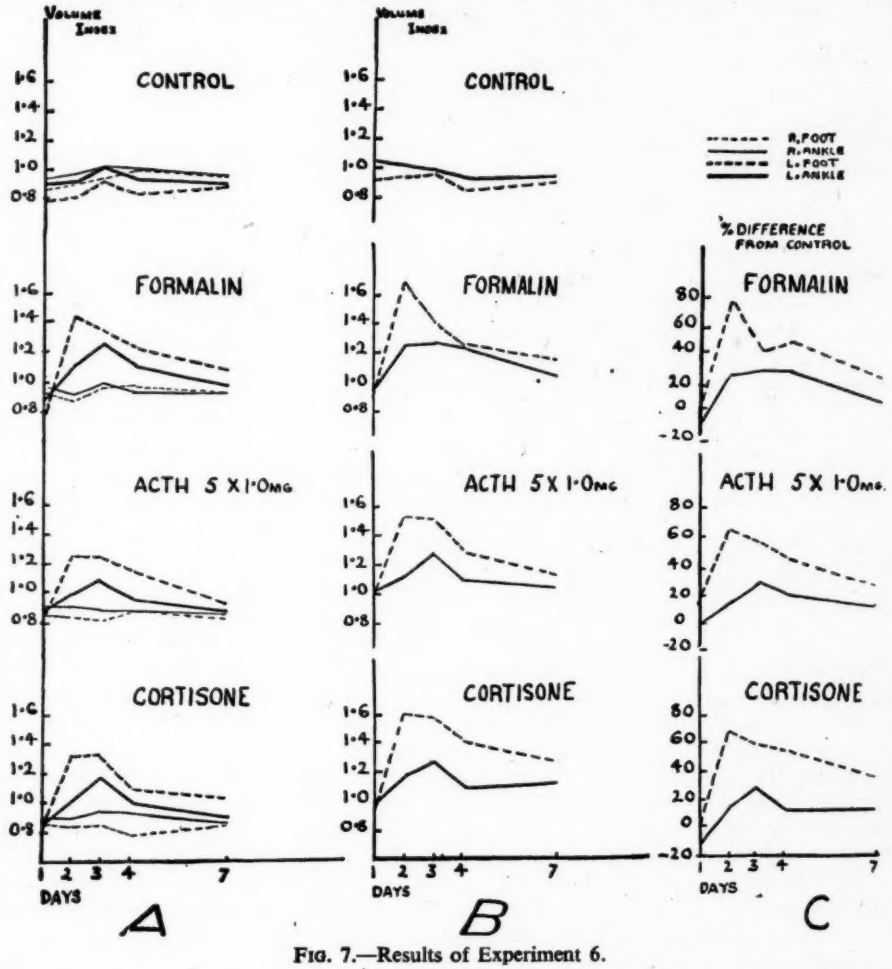

FIG. 7.—Results of Experiment 6.

As the rats had not been weighed every day a correction was sought by comparing the ratio between the volume of the injected and uninjected limb for the different groups. It will be seen from the results given in Fig. 7,B that when this was done there still remained an apparent protective effect of both cortisone and A.C.T.H.

The results in Fig. 6,A show that a similar decrease in volume of the uninjected limb as compared with that of the control group also occurred in the group treated with cortisone in Experiment 5, although without great loss in body weight. Correction of these results has not been made, as this would even further emphasize the ineffectiveness of the treatment.

Discussion

In our experiments a group of completely untreated rats has been followed as a control for day-to-day measurements of limb volumes, and the amount calculated by which each measurement for a formalin-injected group exceeded that for the control group, expressed as a percentage of the latter (Figs. 3,B–6,B).

In Experiment 6 the values plotted in Fig. 7,C are similarly derived from the ratios of injected and uninjected limbs.

Two methods have been used in testing the significance of our results:

1. The "t" test has been applied to differences between the values for treated and untreated groups in Figs. 3,B–6,B and 7,C, to obtain values for P (Table I).

As used here, this test essentially reveals *consistency* of difference—that is, whether the values for one group are consistently greater or smaller than the values for another. Values for P less than 0.05 correspond to significantly consistent differences, but it will be seen that the results do not always bear out the impressions recorded above. Nor is the significance for the effectiveness of the treatment clear in every case (e.g., uninjected limb, Experiment 2).

2. Any treatment should produce a certain *degree* of difference between treated and untreated groups before effect can be claimed. In order to determine if any of the differences observed were of significant amount we compared the means of the series of daily measurements for each group, in the form of the "percentage

TABLE I

Experiment	Treatment	Value for P			
		R. Foot	R. Ankle	L. Foot	L. Ankle
2 (Fig. 3,B)	D.C.A.+ascorbic acid	(+)0·035	(+)0·04	(+)0·02	(−)0·02
3 (Fig. 4,B)	A.C.T.H. 2×0·1 mg.	>0·9	0·75	0·3	(−)0·01
	A.C.T.H. 2×0·25 mg.	0·35	0·15	0·7	0·45
4 (Fig. 5,B)	A.C.T.H. 2×1·0 mg.	0·3	0·5	>0·9	(−)0·03
5 (Fig. 6,B)	Cortisone	(−)0·02	0·4	0·4	0·15
6 (Fig. 7,C)	Cortisone	Values for left limb corrected for right limb		0·9	0·15
	A.C.T.H. 5×1·0 mg.			0·85	0·08

For values of P below 0·05: (+) = values for treated group greater than those for untreated; (−) = values for treated group less than those for untreated.

difference from control" (Figs. 3,B–6,B and 7,C). For this purpose we considered the means of such series for all the otherwise untreated formalin-injected groups and calculated from those a further mean, with its deviation. These figures are given in Table II, which shows two such calculations—one for those series of measurements made for four days and the other for those covering two weeks (eight values).

TABLE II.—*Mean Responses for Formalin-injected Groups. Injected Foot Only*

	4-day Period		2-week Period	
	Foot	Ankle	Foot	Ankle
Experiment 2 (Fig. 3,B) ..	36·9	23·0	38·6	31·2
,, 3 (Fig. 4,B) ..	42·4	27·9	44·4	27·4
,, 4 (Fig. 5,B) ..	50·0	37·2	50·3	33·5
,, 5 (Fig. 6,B) ..	38·4	34·0		
,, 6 (Fig. 7,C) ..	37·2	17·5		
Mean	40·9	27·9	44·4	30·8
Standard deviation ..	±5·4	±8·0	±5·25	±3·1
s as % of mean	13·2	29·0	12·0	10·0
Range ±s (P=0·33) ..	86·8–113·2%	71–129%	88–112%	90–110%
Lower limit as % of higher	76·5	55·0	78·5	82·0
Range ±2s (P=0·05) ..	73·6–126·4%	42–158%	76–124%	80–120%
Lower limit as % of higher	58·0	26·6	61·5	66·7

The overall means provide some measure of the variation in response of groups of rats to formalin-injection, by which we may estimate significance of the difference in response produced by any treatment. We may expect that in two out of three experiments any two groups of rats, injected with formalin only, might chance to differ in response by as much as 2s, while in 19 out of 20 experiments the chance difference might amount to 4s. The ratios between the extreme values of such ranges are also given in Table II, where the lower limit is expressed as a percentage of the higher.

Before any significance can be attached to the difference the value for any treated group should be a smaller proportion of that for the untreated group than the ratio given in Table II. The ratios between treated and untreated groups found in Experiments 2–6 are given in Table III, and these may be compared with the above criteria.

We may regard A.C.T.H. in doses of 1 mg. twice daily and 1 mg. five times daily, and also cortisone as given in Experiment 6, as effective (2 to 1 chance) in reducing the severity of the lesions of the ankle over a four-day period. No treatment reduced the condition in the foot, although D.C.A. and ascorbic acid (Experiment 2) may have exacerbated it (>170% of untreated group). With this last exception none of these estimates represents a 19 to 1 chance of certainty. Over the two-week period there appears to be more than a 2 to 1 but less than a 19 to 1 chance that D.C.A. and ascorbic acid exacerbated the condition in the foot, while the same treatment, as well as that of A.C.T.H. 1 mg. twice daily, shows about a 19 to 1 chance of having reduced the condition in the ankle.

Conclusion

We have mainly studied the effects of treatment on the acute condition resulting from formalin-injection. This is particularly true of the later experiments; only in those earlier experiments which lasted more than two weeks could anything approaching a chronic condition be said to have existed. In all these cases we have found that during the last two weeks of experiment the condition, as judged from measurements and appearance, has consistently regressed. Frequently the limbs had returned to normal, or nearly so, by the end of four weeks, although, as noted above, histological examination usually revealed residual abnormalities.

Our experiments do not confirm the statement by Selye (1949) that "self-maintaining chronic inflammatory process" develops in the ankle-joint, showing "little or no sign of regression for weeks after the last injection." Our evidence does not support the claim that D.C.A. and ascorbic acid prevent the development of formalin-arthritis.

In every case this combination exacerbated the acute oedematous response of the *foot*, which we have also observed in animals treated with D.C.A. alone.

This is interesting in view of the experiments of Brownlee (1950), since it is this acute response of the foot which his method of measurement would seem to detect. In the one case where our results indicate that D.C.A. and ascorbic acid reduced the *ankle* response, histological examination showed no corresponding protection.

The possibility exists that the two highest dose levels of A.C.T.H. exerted some protective action on the *ankle*, but, since the condition of the animals in Experiment 6 deteriorated, the results should be treated with reserve.

In Experiment 5 cortisone gave a completely negative result, throwing further doubt on the interpretation of the action of this drug on the ankle observed in the later experiment. Neither cortisone nor A.C.T.H. had any effect on the swelling of the foot.

We can state with certainty that in our experiments neither A.C.T.H. nor cortisone exerted a protective action against "formalin-arthritis" in rats in any way resembling the dramatic effects described by Selye.

TABLE III

	4-day Period				2-week Period			
	Mean Value		Mean Value / Value for Untreated Group %		Mean Value		Mean Value / Value for Untreated Group %	
	Foot	Ankle	Foot	Ankle	Foot	Ankle	Foot	Ankle
Experiment 2 (Fig. 3,B): D.C.A. + ascorbic acid ..	67·1	20·1	182·0	87·5	58·0	19·6	150·0	62·8
Experiment 3 (Fig. 4,B): A.C.T.H. 2 × 0·1 mg. ..	47·0	23·1	110·0	82·5	48·4	23·1	109·0	84·0
A.C.T.H. 2 × 0·25 mg. ..	36·2	25·8	86·0	93·0	43·5	30·3	98·0	100·0
Experiment 4 (Fig. 5,B): A.C.T.H. 2 × 1·0 mg. ..	45·5	41·0	91·5	51·5	52·0	22·5	103·5	67·0
Experiment 5 (Fig. 6,B): Cortisone	43·0	39·1	112·0	115·0				
Experiment 6 (Fig. 7,C): Cortisone	43·9	9·8	118·0	56·0				
A.C.T.H. 5 × 1 mg. ..	44·4	9·1	104·0	52·0				

We therefore conclude that "formalin-arthritis" in rats is unsuitable for use as a screening test for substances proposed for the treatment of the rheumatic diseases.

Summary

Experiments on the production of "formalin-arthritis" in rats have been described.

D.C.A., and D.C.A. with ascorbic acid, A.C.T.H., and cortisone were tested for effect in this condition.

None of these substances used in the doses given, or the experimental conditions employed, prevented the development of the inflammatory response or swelling in the foot, although swelling was exacerbated by D.C.A. whether given alone or with ascorbic acid.

The effects on the ankle response are discussed.

We are indebted to Professor A. R. Todd and Professor F. G. Young, through whose kindness the A.C.T.H. was provided; to Dr. G. H. Bourne for histological details which he supplied in advance of publication; to Dr. F. Bergel for his sustained interest in this work; and to Miss B. O'Brien for technical assistance.

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ACUTE PERFORATION OF GASTRO-DUODENAL ULCER TREATED CONSERVATIVELY

BY

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Acute perforation is a grave surgical emergency which if left untreated will cause death in most cases (Trinca, 1947). In the best surgical hands the overall mortality rate—even when the simplest procedure for closing the perforation was used—was probably in the region of 15 to 18%. However, recent figures (Avery Jones *et al.*, 1950) show that this rate has dropped to 4%. I hope to prove that surgery should no longer play a predominant part in the immediate treatment of gastro-duodenal ulcer perforations. It should be the aim of the surgeon to aid Nature, which after all is a great healer. It will have been noticed, when operating on these patients, that in a large percentage of cases the opening in the duodenum or stomach had already become sealed off. Is it helpful in these cases to open the abdomen and close the perforation that is already sealed off, or in any case will become sealed off very soon?

Taylor (1946) reported a series of 28 such cases which were treated conservatively. In three of the four fatal cases necropsy showed that the perforations had become sealed. In a further series of 73 cases (1951) he had seven deaths, five of which were unrelated to the method of treatment. In every perforation the peritoneal exudate is purposive and protective, and its loss in laparotomy, through spilling over and the use of the swab and suction pump, is a serious thing for the patient, as this exudate contains millions of leucocytes and is, as it were, lying in wait for the bacterial onslaught which takes place in 12 to 18 hours (Davison, Aries, and Pilot, 1939). Admittedly, closing the perforation prevents further leakage, but if continuous suction is used (see below), as distinct from the interrupted suction apparently employed by other writers, there is little possibility of further leakage.

The Method

The routine conservative treatment adopted in the present series of 15 cases, except Case 12, was as follows.

(*a*) Continuous suction, by means of a Ryle's tube attached to a silent electric motor, was maintained till the withdrawn fluid had been bile-stained for about six hours. Such staining is an indication that the pylorus is patent; in other words, spasm has passed off and the usual oedematous condition of the pylorus is cleared up. It is essential to watch the drainage carefully, because the Ryle's tube with its small bore gets blocked very easily. Patency of the pylorus was usually established in from 48 to 72 hours.

(*b*) Intravenous 5% glucose-saline was given. It may be that a hyalase drip would do as well.

(*c*) Morphine, ¼ gr. (11 mg.), six-hourly for three or four doses is all that is required. It was noticed that the excruciating pain became easier in one to two hours after the continuous suction was started. The rigidity had entirely disappeared after 24 hours, but the generalized tenderness remained up to 48 hours, whereas localized tenderness at the site of perforation usually lasted for 72 to 96 hours.

(*d*) Chemotherapy. Penicillin, 40,000 or 60,000 units, was given four-hourly. Cases 3, 4, and 9 were given sulphonamides also. As bacterial peritonitis is the greatest danger to these cases, the use of penicillin is of the utmost importance. In Case 12 chemotherapy was not employed in the early stages, and it is noteworthy that this patient developed a subphrenic abscess, which might possibly have been avoided if chemotherapy had been instituted from the beginning.

(*e*) Deep-breathing exercises.

(*f*) The patient is allowed to take sips of water from the start; this helps to keep the mouth moist and clean, and also seems to lessen the irritation from the Ryle's tube. When the tube is removed, diluted milk is given, and gradually the usual ulcer diet is built up.

Discussion

Fifteen cases of unselected perforated gastro-duodenal ulcer without fatality are recorded. One developed a subphrenic abscess which required drainage. Cases 1, 2, 3, 4, 6, 8, 9, 10, 13, and 14 were kept in hospital longer than necessary simply for observation purposes, but all except Case 7 made a comparatively speedy recovery.

The late Mr. A. Hedley Visick (1946) noted the gradual trend towards conservatism in the treatment of peptic ulcer perforation. Further, he noted four distinct phases in that treatment, the fourth and last being conservative non-operative procedures. It seems to me that this phase has come to stay.

The patients under conservative treatment require on balance less nursing attention—an important point in these days of shortage of nurses. Post-operative shock, post-anaesthetic complications, and wound infection or incisional hernia do not occur. There is no aggravation of the existing peritonitis or trauma of the peritoneum, stomach, or duodenum, and no spread of a localized peritonitis by breaking down any walling-off. Taylor (1951) has however pointed out the serious result of

Details of Cases

Case No.	Sex and Age	Ulcer History	Hours Perf.	Condition on Admission	Days in Hospital	Remarks	Follow-up
1	M 58	Long	13	General condition good. T. 96° F. (35·6° C.), P. 96, R. 24. Tongue dry. Abdomen: no movement with respiration, generalized pain, tenderness, and board-like rigidity; liver dullness present	21	Test meal: hyperacidity	Seen 12 months after perf. Patient still on ulcer diet; not taking medicine in any form. No symptoms since discharge from hospital. Fully employed
2	F 45	1½ years	12	Appeared shocked. T. 101·4° F. (38·55° C.), P. 100, R. 22. Pale; tongue dry. Abdomen: generalized pain, tenderness, and rigidity, very marked in the epigastrium	17	Barium meal showed duodenal erosion and pylorospasm	Seen 10 months after perf. Free from symptoms except at times of dietary indiscretion
3	M 25	1 year	4½	General condition poor. T. 98·4° F. (36·9° C.), P. 106, R. 32. Abdomen not moving with respiration; generalized pain, tenderness, and board-like rigidity. P.R., tender in the pouch of Douglas	18	Straight radiograph of abdomen showed gas under the right diaphragm	Seen 10 months after perf. No symptoms for 6 weeks after discharge. Has had periodic attacks of indigestion ever since, increasing in frequency recently; taking stomach powder, but not sticking to correct ulcer regime. Fully employed
4	M 46	1 week	5½	General condition poor. T. 97° F. (36·1° C.), P. 110, R. 24. Abdomen scaphoid; no movement on respiration; generalized pain, tenderness, and rigidity; no liver dullness	12	Straight radiograph of abdomen showed no free gas under the diaphragm	Seen 9 months after perf., no symptoms since discharge from hospital. On ulcer diet. Has gained 2 stone (12·7 kg.) in weight. Fully employed
5	M 61	Since previous perf. 25 years ago	9	General condition fair. T. 95·6° F. (35·3° C.), P. 90, R. 30. Abdomen: no movement on respiration; generalized pain, tenderness, and rigidity	48	20 days after admission laparotomy confirmed perf. Vagotomy and posterior gastroenterostomy performed	Seen 12 months after perf. on ulcer diet and stomach powder. No gain in weight; feels much better than before perf. Fully employed
6	M 30	14 days	4	General condition fair. T. 97° F. (36·1° C.), P. 110, R. 24. Tongue dry. Abdomen: generalized pain, tenderness, and rigidity; liver dullness absent	12		Has left Lancashire
7	M 45	Long	4½	General condition shocked. T. 95° F. (35° C.), P. 84, R. 24. Abdomen scaphoid; no movement on respiration; generalized pain, tenderness, and board-like rigidity	28	Developed signs of pelvic abscess, which did not require any surgical intervention	Seen 10 months after perf. No symptoms since discharge from hospital. Has gained 3 stone (19·05 kg.) in weight. Fully employed
8	M 38	,,	10	General condition fair. T. 99·6° F. (37·55° C.), P. 88, R. 22. Generalized abdominal pain, tenderness, and rigidity, more marked in the right abdomen. P.R., no tenderness	12	Straight radiograph of abdomen showed gas under right diaphragm	Seen 9 months after perf. Has remained symptom-free since discharge from hospital. On rigid ulcer diet and stomach powder. Fully employed
9	M 33	,,	8	General condition fairly good. T. 98·4° F. (36·9° C.), P. 108, R. 24. Tongue clean and moist. Generalized abdominal pain and tenderness, especially in right epigastric region and right loin. Board-like rigidity. P.R., no tenderness	15	Straight radiograph of abdomen showed gas under right diaphragm, with herniation of small bowel through left diaphragm into the thoracic cavity, which apparently followed injury during the war in Burma	Seen 8 months after perf. Still on ulcer diet. No medicine or powder; no symptoms since discharge from hospital. Fully employed
10	M 32	1½ years	3	General condition fair. T. 97° F. (36·1° C.), P. 90, R. 20. Abdomen scaphoid; slight movement on respiration; generalized pain and tenderness, maximum in the epigastric region, marked rigidity. P.R., no tenderness	14	No free gas under the diaphragm shown on radiograph	Seen 8 months after perf. On ordinary diet has periodic attacks of indigestion, but not as severe as before perf. Fully employed
11	M 43	Not elicited		General condition fair. T. 98° F. (36·7° C.), P. 100, R. 20. Generalized abdominal pain and tenderness, especially in the epigastric region. Abdominal muscles held very rigidly. Patient would not co-operate	14	Neurasthenic; impossible to obtain correct history. Test meal hyperacidity. Barium meal before discharge showed spasm of pyloric antrum and duodenal bulb, indirect evidence of duodenal ulceration	Seen 13 months after perf. "Sticking as near as possible to ulcer diet." Gained 7 lb. (3·18 kg.). No symptoms of indigestion since discharge. Fully employed
12	M 40	Long	6	General condition poor. T. 97° F. (36·1° C.), P. 88, R. 20. Pain, with anxious expression. Tongue dry and coated. B.P. 130/80. Abdomen: no movement on respiration; generalized pain and tenderness, especially marked in left upper abdomen. Liver dullness present	49	Gastric ulcer perf. 14 days later, anterior subphrenic abscess drained; large gastric ulcer seen on lesser curve. This was adherent to liver and well sealed off. Condition on discharge satisfactory	Seen 18 months after perf. No symptoms except when "I go off the diet." Has gained weight. Smokes heavily. No alcohol. Fully employed
13	M 21	No ulcer history	2	General condition fair. T. 100° F. (37·8° C.), P. 96, R. 26. Abdomen: appendicectomy scar; generalized pain, tenderness and rigidity, most marked over pylorus. Chest: rhonchi and rales	15	Suffered from asthma and bronchitis and was a bad operative risk	Seen 14 months after perf. Still suffering from asthma. "Careful in diet." No symptoms since discharge from hospital except when overworking
14	M 48	Long	9	General condition fair. T. 100·4° F. (38° C.), P. 88, R. 20. Tongue dry and coated. Abdomen: generalized pain, tenderness, and rigidity most marked in epigastric region. Release tenderness marked in lower abdomen. Liver dullness present	21	6 years previously, posterior gastro-jejunostomy and gastric ligation performed for indurated ulcer of first part of duodenum. Appendicectomy. Test meal: hyperacidity. Barium meal before discharge: no stomal ulcer seen. Duodenal bulb irregular, slightly tender, active duodenal ulcer suggested	Seen 18 months after perf. Free from symptoms until very severe attack of indigestion 3 months ago. Not dieting. Has very irregular meals because of work. Takes stomach powder on and off. Smokes heavily. No alcohol. Fully employed
15	F 36	2 years	8	General condition poor. T. 97° F. (36·1° C.), P. 96, R. 22. Generalized abdominal pain, tenderness, and rigidity, most marked in right side of abdomen. Liver dullness absent	14	Radiograph showed gas under the right diaphragm	Not traced

All the above cases showed the usual signs of peptic ulcer perforation.

unrecognized air swallowing in the aspiration method of treatment. There are no post-operative chest complications, so common after operation for perforation. It may be that the risk of subphrenic abscess will be reduced, if not entirely eliminated, for it is likely that the patient's increased respiratory excursions while under the influence of the anaesthetic can, by suction, fill the subphrenic spaces with peritoneal exudate.

What the ultimate fate of these patients will be it is not possible to say at present. So far only Case 5 has been submitted to operation. All the others left hospital symptom-free, though of course on strict ulcer diet. Case 12 should certainly be subjected to gastrectomy if the gastric ulcer is still present on review. If and when gastrectomy or other operative procedure is required in any of these cases it is to be expected that easier operating conditions will be found than would be the case if a laparotomy had already been performed.

It will be noted from the follow-up that 13 of the 15 cases were seen on the average almost 12 months after perforation, and that their condition was at least no worse than if they had been subjected to an immediate operation. The above series of cases is admittedly a small one, but, even so, I would suggest that immediate operation in simple gastro-duodenal perforation is no longer necessary, and that any operative intervention should be reserved for such complications as may arise. Since this paper was written further cases have been similarly treated with equal success.

I wish to thank Mr. J. C. Jefferson for the watchful eye he kept on the patients and for his help and criticism of this paper; also Dr. T. Benson, house-surgeon, for his enthusiastic co-operation.

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MACROCYTIC ANAEMIA

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The aetiology and treatment of macrocytic anaemia have in recent years been the subject of much investigation, both clinical and experimental. The following case of macrocytic anaemia cured by surgery gives support to the experimental conclusions.

Literature

In 1897 Faber first reported the association of anaemia with gross intestinal disease; many attempts have since been made to relate intestinal disease in human beings, and conditioned disease in animals, to the aetiology of macrocytic anaemia. Anaemia in human beings has long been familiar as a complication of gastrectomy and of resection of the small bowel. It seemed probable that this anaemia is due to an unaccustomed dietary regime and to the hurried passage of the bowel contents in the changed circumstances. In fact, however, experimental resection of varying lengths of the gut, including in some cases the stomach, failed to produce a macrocytic anaemia in animals. Miller and Rhoads (1935), working on dogs, succeeded in producing only "a mild hypochromic anaemia," while Brown (1938) concluded that "resection alone did not lead to diarrhoea, anaemia, or paralysis." Wintrobe *et al.*, (1939) found that removal of the duodenum with a portion of the jejunum in addition to the stomach resulted in microcytic anaemia. Jensenius (1945) reviewed the literature and carried out a carefully controlled series of experiments on dogs. He concluded that resections of the terminal ileum may be followed by a macrocytic anaemia or a tendency to such.

It therefore seemed that lesions of the proximal gut would tend to produce a microcytic anaemia, and that lesions of the distal bowel would tend to produce a macrocytic type.

Seyderhelm *et al.* (1924), by inducing fibrous strictures of the terminal ileum, were able to produce a macrocytic anaemia in two of seven dogs that survived the operation. They decided that "an abnormal bacterial flora in the small intestine was decisive in the development of the anaemia." Tönnis and Brusis (1931) achieved the same results and attributed the anaemia to autointoxication, which could be relieved by the removal of the affected loop of intestine.

It is to be noted that these experiments introduced a new element, that of partial obstruction as distinct from resection of the bowel. These observations, made by Seyderhelm *et al.* more than twenty years ago, are in accordance with the present belief that a disturbance of the normal fermentative processes in the small intestine and colon results in the failure of production of folic acid and of vitamin B_{12}, with the consequent development of a macrocytic anaemia.

Cartwright *et al.* (1946) produced abnormal intestinal conditions in pigs by withholding folic acid, para-aminobenzoic acid, and inositol, and giving succinylsulphathiazole and a folic-acid antagonist. The four pigs used became weak and listless, with loss of appetite; growth was poor, and diarrhoea developed; in three to six weeks an anaemia, macrocytic in type, with a megaloblastic bone marrow, supervened, which responded to folic acid but not to liver.

In an attempt to find a laboratory animal in which an experimental macrocytic anaemia could be produced at will for assay of therapeutic preparations, Watson, Cameron, and Witts (1948) operated on rats, producing a blind antiperistaltic intestinal loop, and by this means succeeded in inducing a macrocytic (megaloblastic) anaemia.

Since Faber's early observation of the association of anaemia with intestinal disease in humans many clinicians have reported cases in which regional lower-intestinal lesions have been associated with macrocytic anaemia. Barker and Hummel (1939) analysed 51 cases of macrocytic anaemia in which the primary lesion seemed to be intestinal strictures or faulty anastomosis. They suggest that the pathogenesis of this form of anaemia is intimately connected with stagnation and putrefaction of the intestinal contents, resulting perhaps in the absorption of toxins, and that the haemopoietic liver principle may act as a detoxicator of these

substances rather than as a catalyst of red-cell maturation. They point out that the treatment of the syndrome depends on the surgical extirpation of the cause of stagnation.

We believe the case here recorded to be of interest in that it provides the analogy, in respect of aetiology, treatment, and results, to the animal experiments of Professor Witts. In both cases a blind antiperistaltic intestinal loop was produced, a macrocytic anaemia resulted, and the anaemia was cured by excision of the loop in the human, without recourse to folic acid or liver.

Case Report

An electrical engineer aged 35 attended hospital on September 3, 1948, complaining of colicky pains in the abdomen of one year's duration. The pain was felt almost immediately after meals and was accompanied by severe flatulence. There had been no vomiting, and the appetite was about average. The bowels were regular, with no diarrhoea. He also complained of cramps in the legs and of sweating profusely. There had been considerable loss of weight, as evidenced by his clothes.

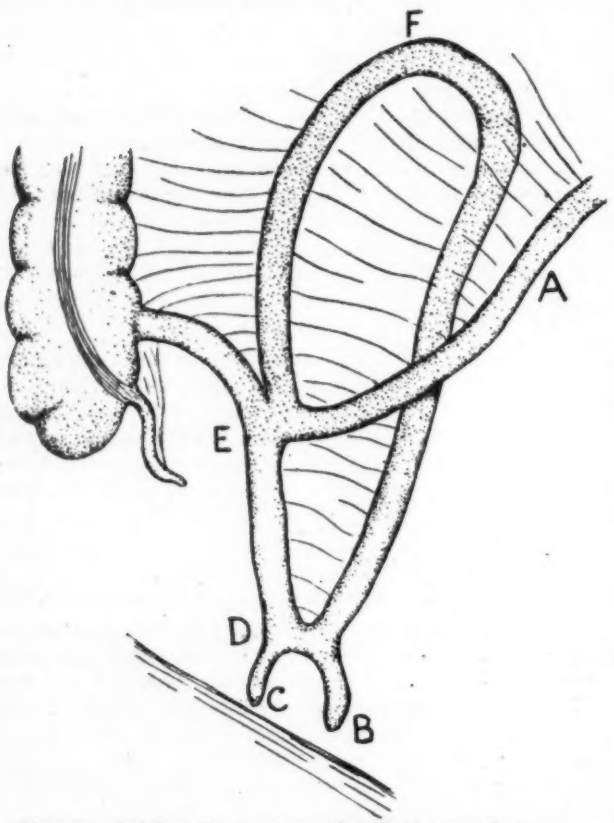

Diagram showing the anatomy found at operation. A = proximal loop of terminal ileum. B = blind end at inguinal ligament. C = blind end of distal loop. D = fistula between proximal and distal loops. E = entero-anastomosis. F = twisted blind loop.

In 1942 he had been admitted to another hospital with a strangulated inguinal hernia of some days' duration. At operation gangrenous bowel had been found, and, after laparotomy, a Paul–Mikulicz resection had been performed. After prolonged convalescence he had returned to work and had remained in reasonable health until one year before the time of examination.

He was thin almost to the point of emaciation, was pale and listless, and showed clinical evidence of anaemia. His tongue was normal; his finger-nails were brittle, and there was possible early clubbing of the fingers. The abdomen was thin-walled and protuberant, especially in the lower right quadrant. Coils of distended bowel were palpable in the lower abdomen, and irregular waves of peristalsis could be seen. On September 3 his blood count was: Hb, 76% (10.49 g.%); red cells, 3,090,000 per c.mm.; colour index, 1.2; mean diameter, 7.6 μ; anisocytosis, ++; M.C.V., 113 μ^3; M.C.H.C., 29.99%; leucocytes, 4,800 per c.mm. (polymorphs 40%, lymphocytes 51%, monocytes 9%); E.S.R., 2 mm. in one hour; icterus index, 7 units; blood sugar, fasting, 77 mg. per 100 ml. A test meal showed sustained hyperchlorhydria.

A diagnosis of subacute intestinal obstruction of small-bowel type was made, and on October 31 a laparotomy was performed.

The abdomen was opened through a lower paramedian incision, and distended small bowel presented in the wound. The right iliac fossa was a mass of adhesions, and the anatomy was finally demonstrated only after considerable dissection and with some difficulty. When finally displayed the position was found to be as follows. At about 3 ft. (0.9 metre) from the ileo-caecal valve the proximal loop of the terminal ileum ran down to a blind end at the internal inguinal ring (see Diagram). About 2 in. (5 cm.) above the internal ring a fistulous opening connected the proximal loop to the distal loop of terminal ileum, which also terminated in a blind end at the internal ring. About 6 in. (15 cm.) above this fistula an entero-anastomosis had been performed. In carrying out the anastomosis the proximal loop had been rotated through 180 degrees before being united to the distal loop, thus producing an antiperistaltic anastomosis.

The contents of the intestine therefore passed down the proximal loop of ileum, through the fistula, up the distal loop of ileum to the entero-anastomosis, and so back into the proximal loop in a circus movement. The terminal ileum distal to the anastomosis and the caecum were collapsed. Numerous very large soft glands were present in the mesentery.

After some consideration the entire complex was resected *en masse*, and a side-to-side enterocolostomy performed immediately distal to the caecum. Convalescence was surgically uneventful.

After operation the blood count rose to normal of its own accord. On December 13 the blood picture was: Hb, 98%; red cells, 5,230,000; C.I., 0.94; mean diameter, 7.15 μ.

Up to the time of his last visit to the follow-up clinic, January, 1950, this improvement had been maintained.

Comment

This case differs from those reported by Barker and Hummel and by others in the nature of the causative lesion. In this instance the essential pathology was not a stricture of bowel due to trauma, disease, or an inadequate stoma, but an antiperistaltic anastomosis causing virtually a blind loop, and thus stagnation of the bowel contents. It was in fact precisely the distortion which had been produced deliberately in rats in order to induce a macrocytic anaemia.

All of the 51 cases of lower-intestinal lesions analysed by Barker and Hummel showed anaemia, but 42 presented with gastro-intestinal symptoms; 25 had glossitis, in 4 glossitis was absent, and in 22 glossitis was not mentioned. Macrocytosis was found in 39 cases, and 11 were stated to be suffering from pernicious anaemia: one case showed no macrocytosis. Hyperchromia was recorded in 32 out of 42 cases, while leucopenia was present in 30 cases, absent in 6, and not mentioned in 15. Free hydrochloric acid was present in 17 cases, absent in 19, and not recorded in 15.

Our patient presented with loss of weight and gastro-intestinal symptoms. Anaemia was clinically obvious. Examination showed a macrocytosis with a megaloblastic

bone marrow, neutropenia, and hyperchlorhydria. He stated that his tongue had been sore, but examination showed no abnormality.

The anaemia was undoubtedly due to stagnation of bowel contents interfering with the normal fermentative processes in the ileum, affecting folic acid and/or vitamin-B_{12} production. The recent work of Dyke *et al.* (1950) would seem to support this contention, more particularly if it can be assumed that the effects of the stagnation would extend to include the colon with consequent folic acid and vitamin-B_{12} deficiency.

Summary

A case is presented of a man aged 35, with loss of weight, gastro-intestinal symptoms, and a macrocytic anaemia, which seems to give clinical support to experimental work on the aetiology of macrocytic anaemia. It is noteworthy that the condition developed after surgical procedures which led to small-bowel stasis, and was cured by surgical removal of the lesion, without recourse to liver, folic acid, or vitamin B_{12}, which were not necessary in order to effect a readjustment of the normal intestinal metabolic processes and of the normal relationship between host and intestinal bacteria.

This case and a study of the literature emphasize again the necessity for a complete intestinal investigation in all cases of macrocytic anaemia which do not fall into well-recognized clinical groups, such as Addisonian anaemia, the macrocytic anaemia of pregnancy, or those associated with diagnosed constitutional disease.

It seems that short-circuit operations below the stomach are unsound except as a temporary measure. This is particularly the case when an antiperistaltic anastomosis is fashioned. There is a danger of the development of a macrocytic anaemia in such procedures as ileo-colostomy, in which a blind length of bowel is left.

The literature is reviewed.

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In the annual report for 1949 of the Medical Department of the Uganda Protectorate there is a description of the methods by which information is obtained about the state of public health in the Protectorate. Some of the notifications of deaths and of infectious diseases are made by chiefs of tribes, and, though the total deaths notified in this way are reasonably accurate, the allocation of deaths to the primary cause leaves much to be desired. The compiler of the report writes: "While the infectious diseases are generally diagnosed accurately, many deaths from 'old age,' 'chest,' or 'njoka' (literally, a snake in the stomach) afford little information about the real cause of death. Less than one-twentieth of all deaths occur in Government hospitals, and it is rare for deaths outside to be attended by medical practitioners."

Medical Memoranda

Pericardial Effusion as a Sequel to Subphrenic Abscess

The rarity of pericardial effusion as a sequel to subphrenic abscess has prompted the recording of this case. Of 182 cases of subphrenic abscess reviewed by Harley (1949), none were complicated by pericarditis. Ochsner and De Bakey (1938), reviewing the world literature, recorded pericarditis as a complication in 5% of 1,380 cases. This incidence, which largely results from one series of cases, is probably above the average.

Case Report

On June 4, 1948, a boy aged 11 was admitted to hospital with a 36-hours history of abdominal pain. Operation revealed a gangrenous appendix with pus in the peritoneal cavity. Appendicectomy was performed and the peritoneum drained. During the next three weeks two further abdominal abscesses were evacuated. As his fever persisted he was screened, and this showed the right dome of the diaphragm to be raised and immobile. An anterior subcostal incision was made and two pints (1.14 litres) of pus were obtained from the lateral and superior aspects of the liver. On culture this grew coliform organisms, non-haemolytic streptococci, and *Staphylococcus albus.*

On August 17, as these measures were not entirely successful, 6 in. (15 cm.) of the tenth rib was resected posteriorly. The diaphragm was incised through a transpleural approach. Adhesions were broken down and a cavity was found lying well towards the midline. Thick pus was removed and the site drained. His condition steadily improved, and on September 27 he was discharged. While in hospital he had received 18,200,000 units of penicillin and 64 g. of sulphadimidine.

Three weeks after discharge he vomited and complained of headache, which was later associated with severe upper substernal pain. After one week in bed he felt better.

Three weeks later he was readmitted to hospital following a recurrence of the pain. Clinical findings suggested the presence of a pericardial effusion. In particular, the apex beat could not be seen or felt and the area of cardiac dullness was greatly increased. The heart sounds were notably faint. An electrocardiogram showed no abnormality. Screening revealed a grossly enlarged heart shadow with little movement. The lung fields were clear. A needle was inserted in the fifth left intercostal space, 1 in. (2.5 cm.) medial to the anterior axillary line, and 300 ml. of greenish-yellow opalescent fluid removed. This contained lymphocytes and polymorphonuclear leucocytes in equal numbers and was sterile on culture. The effusion recurred during the next three days, but by the end of a week had receded to normal.

Three weeks later he complained of substernal pain and the effusion was found to have recurred. A small right-sided pleural effusion was also noted—a new feature. The pericardial fluid had the same characteristics as before. The symptoms and signs gradually receded over the next five days.

He remained well until the beginning of February, 1949—an interval of two months. On this occasion the effusion appeared on the day after he had been allowed up for the first time. Bilateral small pleural effusions were also present. He improved with rest. At this point he was given 1 g. of streptomycin daily for eight days. He has had no episodes of pericarditis since.

He was last seen on December 19, 1949, when there was no clinical or radiological evidence of pericardial or subphrenic disease.

Comment

The four attacks of pericarditis with effusion were considered to be secondary to the subphrenic abscess. Although two loculi of pus were drained, a small focus must have persisted. It is unlikely that there was a direct invasion of the pericardium, as the fluid was repeatedly sterile on culture. The effusion is probably analogous to the oedema surrounding any acute inflammation. The immunity of the pericardium, as compared with the pleura, to involvement by subphrenic inflammation may be due to its relation to the avascular central tendon of the diaphragm.

In conclusion, the importance of early diagnosis and treatment of subphrenic infection is again stressed.

I am indebted to Professor J. Craig and Mr. G. Gordon Bruce for help and criticism.

A. L. SPEIRS, M.B., M.R.C.P.

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An Adreno-renal Syndrome in Malignant Tertian Malaria

The patient whose case is described below developed algid malaria in Co. Down after living with impunity in West Africa for 20 years. It could be postulated that during his journey home he was infected with a different strain of *Plasmodium falciparum*, to which he was not immune. Certainly his peripheral blood showed evidence of a heavy infection with the parasite.

Case Report

The patient, a man aged 41, had lived in West Africa since 1930. He was flown home at the end of August, 1950. When seen on September 16 he was in a grave condition, which, by clinical and pathological interpretation, was found to be a state of uraemia arising as the result of a heavy infection with malignant tertian malaria. Before examination he had had preliminary symptoms of pains in the limbs and general fatigue. His illness can be described in two phases—that of serious peripheral vascular failure, followed by the phase of uraemia with deepening coma.

During the first phase the patient was mentally alert and complained bitterly of severe pains in the arms. On examination his whole body, and especially the limbs, was cold and sweaty, and the joints of his right arm were swollen and painful. It was almost impossible to feel his pulse and to record the blood pressure. The systolic blood pressure was below 60 mm. Hg. His temperature was 95° F. (35° C.) and his spleen was greatly enlarged. A sample of urine was found to be free from albumin. At this stage an electrocardiogram showed normal complexes in the standard limb leads and in unipolar chest leads, and an emergency radiograph of the chest revealed a normal heart and lungs. It was therefore evident that he was in a state of grave circulatory failure of peripheral origin, with hypotension as an outstanding feature, and, at the beginning, a normal urine. Appropriate stimulants were given for his state of collapse.

The next day the second stage of the illness had begun. He gradually passed into a state of coma, from which he could scarcely be aroused. An extensive haemorrhagic skin rash developed on the limbs and in the folds of the groins. Marked oliguria occurred, and his urine was loaded with albumin. The following tests were carried out to determine the cause of his coma.

Investigations.—Blood urea, 120 mg. per 100 ml. Blood slides (thick and thin): accolé forms of *Plasmodium falciparum* and male and female gametocytes in abundance; neither trypanosomes nor *Treponema recurrentis* were seen. A hanging drop of blood contained no trypanosomes. Blood counts: red cells, 3,740,000; Hb, 70% (Haldane); white cells, 7,800 (neutrophils 50%, eosinophils 24%, lymphocytes 22%, basophils 2%, monocytes 2%). Urine: albumin +, no casts, no red cells, no haemoglobin, no ova. Weil-Felix OX2, OX19, OXK were negative in all dilutions. The Widal reaction was negative for the salmonella group Agglutination tests for *Leptospira icterohaemorrhagiae*, *Leptospira canicola*, and other West African species of leptospira were negative.

The second phase was therefore characterized by disturbance of renal function with albuminuria and urea retention. As the patient ultimately made a complete recovery and the condition responded dramatically to proguanil, it is reasonable to assume that the heavy malarial infection was responsible for the renal damage, especially as other likely causes had been excluded. Proguanil, 200 mg. daily, was given, and in a few days he made a dramatic recovery. Within seven days his temperature, which had risen at the beginning of the second phase, had settled down, the urinary output was normal, and the urine was free from albumin. All parasites had disappeared from the blood. Later, renal-function tests showed normal function and intravenous pyelography revealed normal kidneys with good concentration power.

Comment

The clinical description of this case of malignant tertian malaria is divided into two distinct phases. The first phase, with its marked hypotension and cold extremities, resembled an acute hypoadrenalism. Significantly there were no urinary changes, and the pain and swelling of the joints are interesting in view of the relation of arthritis to the adrenal glands. Unfortunately, details of electrolytic balance are not available At any rate, the cardiovascular phenomena were peripheral in origin.

The second stage of the illness has two possible explanations. The albuminuria and features of uraemia may have been due to actual involvement of the kidney by malarial infection—that is, a true glomerulonephritis or nephrosis due to tubular damage—or they may have been due to a dynamic disturbance of renal function consequent on the very low blood pressure of the first phase. It is significant that, although the urine was loaded with albumin, repeated microscopical examination failed to show the presence of red blood cells or casts. Thus the urine did not indicate the presence of glomerular inflammation or rupture of capillaries as would have been expected had a true glomerulonephritis been present. The absence of casts in the urine and the raised blood urea do not suggest a primary nephrosis.

In the first phase the marked and persistent hypotension would be sufficient to cause the second phase of the illness with impairment of renal function due to interference with glomerular filtering pressure, the albuminuria being due to the state of anoxia consequent on the reduced renal blood flow. The urine showed a sharp onset of albuminuria, which cleared up abruptly with treatment. This also supports the dynamic theory, as a true nephritis would most likely have shown a persistent albuminuria for some time even after the acute inflammation had cleared up. Moreover, a few weeks later there was no evidence of renal disease.

Acknowledgment is made with gratitude to Dr. C. Murdock, of the Northern Ireland Public Health Laboratory, for help with pathological investigations.

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Reviews

CEREBRAL ANGIOGRAPHY

Cerebral Angiography. By P. Almeida Lima. Foreword by Sir Hugh Cairns, K.B.E., D.M., F.R.C.S. (Pp. 221; illustrated. £2 5s.) London: Geoffrey Cumberlege (Oxford University Press). 1950.

Professor Lima's interest in this subject dates back to 1926, when he assisted Professor Moniz at its inception. The book is based on a personal experience of over 2,000 angiographies and written by a clinician who uses the method when "clinical examination has indicated this necessity." This book is profusely illustrated and the skiagrams have on the whole been well reproduced. The chapter on technique was written in 1946; at that time thorotrast was still the chosen medium and the injection was made after operative exposure of the artery. Because of the need to keep the dose of medium to a minimum, antero-posterior projections were not carried out as a routine, but three consecutive lateral films on each side were considered essential. Professor Lima places great emphasis on the need for three films in order to demonstrate all phases of the circulation, which may be delayed in some circumstances. His pictures fully support his contention. A necessary introduction to the study of vessel displacement caused by tumours is the account of normal angiograms, and repeated reference to this chapter is a wholesome exercise. Many useful points in the topographical diagnosis of tumours are brought out.

Perhaps the most useful part of the book is that on the diagnosis of the histological nature of the tumour, to which Professor Lima has given much study. This depends on recognizing the pattern of the irrigation of the tumour. The characteristics of a meningioma comprise a central zone of abundant capillaries and arteries collecting into a well-formed and clearly defined network of veins on the surface of the tumour. In sharp contrast are those of a glioblastoma—absence of well-formed limits, marked vascular deformities, including arteriovenous communications, and abnormalities of the vessels spreading over a wide area of the brain. In slowly growing gliomas there is usually an extensive avascular area with perhaps a small central core of abnormal vessels. These changes are all well exemplified in the illustrations. Other lesions, such as arteriovenous malformations, aneurysms, subdural haematoma, carotid thrombosis, are also described.

Professor Lima's book will be read with interest and advantage by all who carry out this valuable procedure—one which he himself has done so much to perfect. As well as thanking him for the information it contains, we should like to congratulate him on writing a book in such excellent English.

D. W. C. NORTHFIELD.

AIR STUDIES OF THE BRAIN

The Abnormal Pneumo-encephalogram. By Leo N. Davidoff, M.D., and Bernard S. Epstein, M.D. (Pp. 506; 695 illustrations and 289 figures. £5 5s.) London: Henry Kimpton. 1950.

It is 32 years since Walter Dandy introduced pneumoencephalography as an aid in the diagnosis of neurological disorders. More recently cerebral angiography has been developed. This book makes a welcome appearance at a time when the possibilities of angiography are being explored, and it should be emphasized that these two methods of investigation are complementary: many problems may be solved satisfactorily only by careful air studies. It is dedicated to the memory of Dr. Cornelius Dyke, who was a co-author in the companion volume published earlier, *The Normal Encephalogram*.

This book includes much more than the title implies. The authors discuss both ventriculography and encephalography as well as the plain skiagrams of the various lesions. There are in addition over a hundred illustrative case histories and a chapter on the pathology of brain tumours. These features emphasize the authors' teaching that the skiagrams can be fully interpreted only in the knowledge of all the available facts and that there should be the closest co-operation throughout between the clinician and the radiologist. The recommendation that the training of a neuroradiologist should include an adequate background in neurology and neuropathology will receive general approval.

The main discussion is, very properly, on tumours, but the authors also consider the air studies in a wide variety of neurological diseases. They draw on 20 years' experience and present a statistical survey of 500 brain tumours. There is a good chapter on subdural haematoma, but other post-traumatic changes and complications are less fully described; these sections, together with that on intracranial infection, might well be expanded in future editions. There are nearly 300 illustrations, and on the whole the difficult task of reproducing pneumo-encephalograms has been well done. Some of the pictures are rather small, and this is particularly a disadvantage where changes in the third and fourth ventricle and aqueduct are described; here the use of explanatory line drawings would be helpful.

The book is well produced and there is an excellent review of the literature in each section. With its companion volume it is a fitting testimony to the careful work and many contributions the authors have made in this field.

WALPOLE LEWIN.

COMMON FRACTURES

The Closed Treatment of Common Fractures. By John Charnley, B.Sc., M.B., F.R.C.S. (Pp. 190; 133 figures. £1 15s.) Edinburgh: E. and S. Livingstone. 1950.

This book is written primarily for the resident casualty officer. The author's aim is to teach the relatively inexperienced surgeon how to apply essential mechanical principles to the practical task of reducing the common fractures and holding them reduced. He suggests—and there is no doubt that it is true—that the young surgeon may be fully conversant with the modern textbooks on fracture treatment and yet be unable with any degree of certainty to reduce many of the ordinary fractures. His object has been to fill this gap in education, and he has achieved it with conspicuous success.

The treatment of a fracture is largely a problem of mechanics, and the first chapter is devoted to a simple explanation of the principles involved, which are derived merely from the application of common sense. Yet there is much that will seem new to many readers simply because they have not thought these things out for themselves. The author rightly emphasizes the importance of remembering the unseen soft-tissue structures and assessing their integrity. A chapter on the problems

of joint stiffness is stimulating, and there is a useful account of plaster-of-Paris technique.

In the second and major part of the book the author describes the conservative treatment of all the common fractures from a strictly practical point of view. The methods advocated will, with few exceptions, be endorsed by most orthopaedic surgeons, and there are few minor points to criticize. The section on fractures of the fingers leaves the impression that all phalangeal fractures should be immobilized for three weeks—surely an undesirable doctrine for the young surgeon, who should learn rather that some finger fractures need no immobilization at all. And if in distant old age the author himself is unfortunate enough to fall down and sustain a trochanteric fracture it may be that he will elect to walk again after three months at the risk of incurring some degree of coxa vara, rather than dodder about on crutches trying to avoid bearing weight on the limb "for at least six months" as he now advocates for others.

The illustrations and the production as a whole are first-class, but the text is marred by an irritating excess of italics and bold type, which presumably are meant to give emphasis but which in reality give too little credit to the reader's intelligence.

The book is a notable contribution towards the better treatment of fractures, and it should be read by all who have to deal with these injuries in their recent, tractable phase.

J. CRAWFORD ADAMS.

TEXTBOOK OF OBSTETRICS

Williams' Obstetrics. By Nicholson J. Eastman. Tenth edition. (Pp. 1,176; illustrated. No price.) New York: Appleton-Century-Crofts, Inc. 1950.

Williams' Obstetrics dates from 1902 and is one of the famous products of the Johns Hopkins Medical School. For its seventh, eighth, and ninth editions it depended on the late Professor H. J. Stander, of New York. Now, however, it returns to its original home to receive careful guidance in modern ways at the hands of Professor N. J. Eastman and his staff, the assistance of the latter being generously acknowledged by the author. It is claimed that in this edition one-half of the text and one-third of the illustrations are new. Despite extensive rewriting and drastic cutting of the historical sections (necessary to keep the size within bounds), it is still possible to recognize the style and outlook characteristic of Whitridge Williams himself.

In general and as always the theoretical aspects of obstetrics receive preference over the details of operative technique. When the latter are given the author has resorted to the very useful method of serial diagrams rather than wordy description. Anyone searching for errors and omissions will, of course, find them; they are inevitable in a book of this kind. Some will not be satisfied with the account of the pathology of hyperemesis gravidarum; others will wish to see emphasized the importance of uterine malformation as a cause of malposition of the foetus. It is a nuisance, too, to have to refer to two different sections to learn the management of breech delivery or occipito-posterior position. But the book as a whole is satisfying, and the modernity of its outlook can be gauged by its recognition of the fact that even a dead foetus is sometimes best delivered by caesarean section.

How pleasing it is to learn that Professor Eastman and the authors of the other important American textbooks have now agreed on the use and meaning of certain terms such as engagement and primiparity, and even more pleasing that these conform to the definitions generally applied in Britain. "Whitridge Williams" has for many years been regarded here as one of the two American obstetric classics. The new edition still justifies this viewpoint and easily lives up to the reputation of its predecessors.

T. N. A. JEFFCOATE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Handbook of Biolinguistics: The Structures and Processes of Expression. Part 1, section A. By C. L. Meader, Ph.D., and J. H. Muyskens, Sc.D., L.H.D. (Pp. 330. 63s.) London: Sir Isaac Pitman. 1950.

Tropical Dispensary Handbook. By C. C. Chesterman, O.B.E., M.D., M.R.C.P., D.T.M.&H. 5th ed. (Pp. 313. 12s. 6d.) London: Lutterworth Press. 1951.

Woman: Her Change of Life. By M. Lincoln, M.D., F.A.C.P. (Pp. 116. 6s.) London: Williams and Norgate. 1951.

Problems in Cerebellar Physiology. By G. Moruzzi, M.D. (Pp. 116. 23s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

Recent Advances in Diagnostic Psychological Testing. Edited by M. R. Harrower, Ph.D. (Pp. 120. 20s.) Oxford: Blackwell Scientific Publications. 1950.

Epidemiology of Mental Disorder. Papers presented at a round table at the 1949 Annual Conference of the Millbank Memorial Fund. (Pp. 198. 50 cents.) New York: Millbank Memorial Fund. 1950.

Seven Against Edinburgh. By M. Masefield. (Pp. 324. 10s. 6d.) London: William Heinemann. 1951.

The Cry and the Covenant. By M. Thompson. (Pp. 498. 15s.) London: William Heinemann. 1951.

The Anatomy of Man and Other Animals. By D. Stark Murray, B.Sc., M.B., Ch.B., and G. M. Jeffree, B.Sc. (Pp. 158. 18s.) London: Watts. 1951.

The Biology of Human Starvation. By A. Keys and others. Vols. 1 and 2. (Pp. 1,385. No price.) London: Geoffrey Cumberlege. 1950.

McClung's Handbook of Microscopical Technique. Edited by Professor R. McClung Jones. 3rd revised ed. (Pp. 790. 90s.) London: Cassell. 1950.

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ARTIFICIAL CIRCULATION FOR HEART SURGERY

The recent advances in direct cardiac surgery have led to a great intensification of effort to achieve a successful artificial circulation that will enable intracardiac operations to be done in a bloodless field and at relative leisure. The problems are indeed formidable, and although success has now been achieved with dogs in the experimental laboratory the practical application of this method to man is still a long way off. Even when a successful apparatus and technique have been developed it would seem that the setting up of the independent circulation will in itself constitute a fairly severe operation that may be ill tolerated by patients with disease of the heart.

Prominent among the many workers in this field has been Professor J. H. Gibbon, of Philadelphia, whose first paper on the subject appeared well before the war,[1] and who has made invaluable contributions with his various associates. A recent paper with T. L. Stokes[2] is especially noteworthy because it not only reports the successful survival of eight dogs after complete occlusion of the venae cavae for periods varying from 30 to 40 minutes while an apparatus took over the cardio-respiratory functions, but because it also describes clearly and simply the difficulties that have been met with up to now and explains how they have been dealt with. No one interested in the subject should fail to read this important paper. The authors point out that, although Jongbloed[3] and Dennis[4] have both reported survival of dogs after perfusion of the whole body, neither of these investigators completely interrupted the flow of blood to the heart by clamping the venae cavae. Björk,[5] working with Crafoord in 1948, perfused the brain of a dog with oxygenated blood while both venae cavae were clamped for 33 minutes. Perfusion of the brain alone obviously limits the time during which the venae cavae can be clamped, since other organs—for example, the spinal cord and heart—will be damaged by prolonged interruption of the circulation.

When no septal defect is present the right side of the heart might be opened for an operation by diverting the flow of blood from both venae cavae around the right side of the heart into the pulmonary artery: Sewell and Glenn[6] have recently described a pump for this purpose which they have used successfully in the dog. Again, in the absence of a septal defect, the left side of the heart might also be opened by shunting blood from the left atrium into the systemic arterial system. In each of these cases a single mechanical pump is needed. In the presence of a septal defect two pumps are required for the double extracorporeal circuit. The advantages of short-circuiting blood around the right or left side of the heart lies in the fact that the need for a mechanical lung is eliminated. The difficulty of devising a satisfactory mechanical lung to oxygenate the required amount of blood for use in man is still largely unsolved. Where the shunt is from venae cavae to pulmonary artery the lungs will act as a filter for emboli, which have been shown to be an invariable cause of death if a special filter is not introduced into the stream of blood entering the arteries from the apparatus. Such methods entail opening, cannulating, and subsequently repairing many large vessels within the chest.

The apparatus described by Stokes and Gibbon is relatively simple, but ingenious, and is obviously the result of great and careful study with much trial and error. It contains two pumps, the first of which takes blood from the venae cavae and passes it through an oxygenator, which in the experiments described could introduce 70 ml. of oxygen per minute into the blood. Recently a more efficient oxygenator has been evolved. The second pump delivers the oxygenated blood back into the circulation through a filter and then through a cannula introduced into one femoral artery. The other femoral artery is used for direct estimation of blood pressure, but methods are in use to-day which do away with the need to sacrifice a limb vessel for this purpose. Clotting of blood is prevented by an injection of heparin. At the end of the experiment the effect of the heparin is counteracted by injection of protamine. The apparatus has no valves in order to diminish trauma to cells and turbulence, factors which promote haemolysis and formation of fibrin. Carbon dioxide elimination and acid-base balance are satisfactorily maintained if the gas flowing into the oxygenating cylinder is 96% oxygen and 4% carbon dioxide before the extracorporeal circuit is connected; a change is made to 100% oxygen when the apparatus is in use. A difficult problem to be solved before such a method as this could be applied to man is the sterilization

1 *Arch. Surg.*, 1937, **34**, 1105.
2 *Surg. Gynec. Obstet.*, 1950, **91**, 138.
3 Ibid., 1949, **89**, 684.
4 Contribution at Symposium on Cardiovascular Research, 1950.
5 *Acta chir. Scand., Suppl.*, 137, 1948.
6 *Surgery*, 1950, **28**, 474.

of the apparatus. Stokes and Gibbon clean their apparatus carefully before use, scrubbing all glass–rubber junctions with an alkaline detergent to remove fibrin, and rinsing in a large volume of water. For one hour before perfusion sterile water and then sterile saline are recirculated through the apparatus. No antiseptic solutions are used.

These authors suggest that their apparatus and experiments constitute a step towards the time when the temporary maintenance of the cardio-respiratory function in man may be clinically feasible, both for the purpose of taking over the circulation in patients in emergency states of failing heart or lungs—such as acute coronary thrombosis or acute pulmonary oedema—as well as, ultimately, enabling surgeons to perform precise operations upon the human heart under direct vision in a bloodless field. There can be no doubt that if this is ever achieved a very great advance will have been made, for it will become possible to perform a number of operations, such as closure of septal defects, in a deliberate fashion that is quite impossible to-day. At the same time it must be stated that there are a number of operations that can be and probably always will be done efficiently as " running repairs " without the great extra complexity of establishing an independent circulation. It is just as necessary to study the feasibility of successful running repairs as to strive to perfect an artificial circulation.

THE BLOOD LEUCOCYTES

Since Ehrlich[1] first introduced a satisfactory technique for the differential staining of the white cells of the blood they have been the subject of prolonged study and controversy. One of the earliest of these controversies, still far from being resolved, concerned the genetic relationships of the various leucocytes to one another. Ehrlich[2] himself took strong exception to any attempt at " placing all the leucocytes under one roof," and, in spite of a good deal of evidence which has accumulated during nearly 50 years, similar beliefs could still be expressed by many haematologists, though strongly disputed by others. Apart from the question of the origin of the white cells, there are many other gaps in our knowledge of them. Little is known about the numbers in which they enter the blood and the rate at which they are destroyed in or leave the blood. Nor is much known about their function: the neutrophil granulocyte seems to take pride of place in this respect, though, so far as quantitative data are concerned, more information is available about the lymphocyte than any other of the white cells. This is due to the special relationship between the lymphoid tissues and the lymphatic vessels, by means of which large numbers of lymphocytes reach the blood through the thoracic and right lymph ducts. The lymph in these two ducts can be readily collected, and its lymphocytes estimated, under a variety of conditions. Yoffey[3] has recently reviewed this branch of the subject.

It is possible that the leucocytes are relatively inactive while circulating in the blood. But they are all capable of amoeboid movement in varying degrees, though here again much remains to be learned about the factors controlling this movement.[4] By virtue of their powers of movement leucocytes may pass from the blood capillaries into the surrounding tissues, and, though normally such passage occurs on a small scale only, in certain circumstances it may become greatly intensified. Neutrophils may accumulate in the tissues in enormous numbers at foci of acute bacterial inflammation ; lymphocytes and monocytes may migrate into the tissues in inflammation or during the processes of repair. In these conditions the monocytes may become transformed into macrophages,[5] and it has frequently been claimed that lymphocytes can undergo a similar transformation.[6] Eosinophils may accumulate in the tissues in large numbers in many allergic and other conditions, and there may at the same time be varying degrees of eosinophilia. The significance of changes in the numbers of the blood leucocytes has been assessed on the basis of countless clinical observations, coupled in the case of the neutrophils with their known phagocytic and other properties. But, however useful it may be to count the leucocytes in the circulating blood, such information must necessarily give an incomplete picture of what is happening. A full understanding of the blood picture requires a knowledge of the number of cells which are entering the blood and those which are either being destroyed or leaving it. If either of these two variables is known, then, by taking into account data about the leucocytes in the blood, inferences can be drawn about the other. Unfortunately, it is only with the lymphocytes that even an approximate analysis is possible of the dynamic equilibrium which determines the number present in the blood at any given time. But, even though similar information may not be available in the case of the other leucocytes,

1 " Ueber die specifischen Granulationen des Blutes." *Arch. Anat. u. Physiol., Physiol. Abt.*, 1879, 571.
2 *Anaemia. Histology of the Blood, Normal and Pathologic. In Diseases of the Blood*, 1909, London.
3 *Biol. Rev.*, 1950, **25**, 314.
4 De Bruyn, P. P. H., *Quart. Rev. Biol.*, 1947, **22**, 1.
5 Ebert, R. H., and Florey, H. W., *Brit. J. exp. Path.*, 1939, **20**, 342.
6 Kolouch, F., jun., *Amer. J. Path.*, 1939, **15**, 413.
7 *Endocrinology*, 1944, **35**, 1.
8 Randolph, T. G., *Proc. Soc. exp. Biol., N.Y.*, 1943, **52**, 20.
9 Dunger, R., *Münch. med. Wschr.*, 1942, **57**, 1910.
10 *Blood*, 1948, **3**, 755.
11 *Proceedings of the First Clinical A.C.T.H. Conference*, 1950, London.
12 *Arch. Surg., Chicago*, 1937, **34**, 1049.
13 Whitby, L. E. H., and Britton, C. J. C., *Disorders of the Blood*, 1950, London.
14 Wiseman, B. K., *J. exp. Med.*, 1931, **53**, 499.
15 *British Medical Journal*, 1950, **2**, 286.
16 *Proc. Soc. exp. Biol., N.Y.*, 1950, **75**, 740.

some of the effects of A.C.T.H. on the blood may well lead to much speculation on the subject.

Dougherty and White,[7] in their well-known studies on the action of A.C.T.H. and steroid hormones, noted that single injections of A.C.T.H in mice, rats, and rabbits led within a few hours to an absolute lymphopenia and an increase in the neutrophil granulocytes. They did not observe any changes in the blood eosinophils, for the accurate counting of which special techniques must be employed.[8 9] Hills, Forsham, and Finch[10] were among the first to describe changes in the circulating blood leucocytes in man after the administration of A.C.T.H. Randolph and Rollins[11] reported a marked fall in blood eosinophils between three and five hours after an adequate dose of A.C.T.H., and in company with many other workers came to regard this eosinopenia as evidence of a satisfactory therapeutic response. They further noted an initial transient leucopenia, followed by a leucocytosis with a shift to the left, as well as a lymphopenia. After prolonged (20–30 days) administration of A.C.T.H. the fall in the eosinophils may become less marked and even disappear. There is as yet little information about this "escape phenomenon," nor for that matter about the true significance of the primary eosinopenia. On the whole, in human as opposed to animal studies, interest has centred more on the eosinopenia, which has acquired clinical significance, than on the lymphopenia, which in man has been somewhat variable. It is interesting, however, to note from the literature a frequent association between lymphocytes and eosinophils. Thus Blalock and his colleagues[12] succeeded in effecting complete lymphatic blockage in three dogs. In these three animals it was not perhaps surprising that the lymphocytes disappeared almost entirely from the blood stream; but so, rather unexpectedly, did the eosinophils. Furthermore, while eosinophilia is accepted as a concomitant of many allergic conditions[13] and part of the response to foreign proteins, it is noteworthy that the lymphocyte and the lymphoid tissues also appear to play a part in such responses.[14]

Elsewhere in this issue Professor J. M. Yoffey and Drs. W. K. Metcalf, G. Herdan, and V. Nairn discuss the action of A.C.T.H. and cortical extracts on the lymphoid tissues and the circulating lymphocytes. They paid special attention to the bone marrow, the changes in which are another facet of the problem of the lymphopenia which may follow single injections of A.C.T.H. or cortical extracts. As previously reported,[15] they found no significant changes in the eosinophilic cells of the marrow after these injections. Such a finding need not necessarily mean that the eosinopenia which follows single doses of A.C.T.H. or cortical extract is not due to diminished production of eosinophils by the bone marrow. Rosenthal and his colleagues,[16] in studies on six patients receiving daily injections of cortisone for periods ranging from 2 to 12 days and on one patient receiving A.C.T.H. for four days, found that not only did the marrow eosinophils not decrease but that increases ranging from 42 to 372% occurred at the same time as the blood eosinophils decreased by 64–100%. These findings could conceivably mean that there was interference with the passage of eosinophils from the bone marrow to the blood and that in consequence they accumulated in the marrow, but this is not the only interpretation possible. By way of contrast Bayles and his colleagues[11] found no change in the number of eosinophils in the marrow of a patient with scleroderma treated for 15 days with A.C.T.H., and Goldman and his colleagues[11] reported that in a case of periarteritis nodosa the marrow eosinophils fell from 23% before treatment with A.C.T.H. to 7.6% on the second day of treatment and 0.8% on the tenth day. The meagre reports so far available on the bone-marrow changes in man need to be supplemented before a clear picture of the action of A.C.T.H. on the marrow eosinophils can be built up. With the spate of clinical investigation which is now in progress on the effects of A.C.T.H. there seems little doubt that the information required will soon be forthcoming.

SUPPURATIVE PNEUMONIA

Much of the early confusion in the understanding of lung abscess arose from an undue emphasis on the abscess cavity and a neglect of the study of the primary disease in the lung surrounding the abscess. Thus lung abscess was regarded as a disease instead of an incidental complication in the course of a number of specific pulmonary infections. In more recent years, largely as a result of a series of illuminating papers by Brock in this country[1 2] and Neuhof and Touroff in America,[3-5] various types of lung abscess have become clearly separated as distinct entities. The pathogenesis, course, and treatment of lung abscess due to infection with staphylococci, anaerobic organisms, Friedländer's bacillus, and other organisms, and of those abscesses secondary to bronchial obstruction, have been clearly defined. Certain cases of lung abscess, however, do not fall into any of these categories. In 1938 Scadding[6] drew attention to a condition in which irregular areas of pneumonia broke down into small abscesses and in which the pneumonic process spread to form other areas of consolidation; these in turn

went on to abscess formation or resolution. Scadding regarded this as distinct from other forms of lung abscess and gave it the name of chronic suppurative pneumonia. Neuhof and Touroff,[3 4] describing a similar condition as non-putrid lung abscess, suggested that the difference between this and other lung abscesses was that infection was due to aerobic organisms. Holmes Sellors and his colleagues[7] have fully reported 27 cases of a similar condition under the title of "spreading suppurative pneumonitis." They regarded it as a non-specific pulmonary infiltration leading to cavity formation; and they could trace no definite cause. More recently Logan and Nicholson[8] described 25 cases of non-specific suppurative pneumonia which conformed to the general pattern described by other authors. The onset of the illness was usually abrupt, the initial febrile period lasting for a week or more. Sputum—a constant feature from the onset—was fetid in about half the cases at some stage. A mixture of aerobic organisms was the usual outcome of sputum culture; in no case could a single organism be held responsible for the infection. Radiographs showed that the pneumonia was commonly segmental in origin, but sometimes lobar or scattered in distribution from the start. Spread usually took place by direct extension and was not impeded by the interlobar septa. Less often spread occurred after aspiration of infected material into distant parts of the lung. Treatment was, on the whole, unsatisfactory, the disease often progressing to chronic abscess, pulmonary fibrosis, and bronchiectasis. Pulmonary resection was required in nine cases to eradicate the infection. It should be noted, however, that most cases were seen in the days before penicillin was available.

The aetiology of chronic suppurative pneumonia is not fully understood, and hitherto no explanation of this curious disorder has accorded with the facts. When infected mucus from respiratory inflammation is inhaled into the bronchial tree the severity of the pulmonary reaction depends largely on the virulence of the organisms in the mucus. The most common sequel is a mild pneumonic illness, often referred to as an aspiration pneumonia. At the other extreme, inhalation of virulent organisms will rapidly lead to pulmonary inflammation, gangrene, and abscess. Logan and Nicholson postulated that chronic suppurative pneumonia lies somewhere between these extremes, and that it is, in fact, a severe variant of the aspiration pneumonia so frequently found in association with upper respiratory infections.

In the Goulstonian lectures for 1950 Nicholson[9] put forward further evidence in favour of this theory. He compared a series of 28 cases of suppurative pneumonia from the Brompton Hospital with those referred to above. The clinical features of the later cases were similar to those previously described, but there was evidence that treatment with penicillin brought about a more favourable outcome. Nicholson reviewed the evidence that infected material may be aspirated into the bronchial tree to cause pneumonias of varying severity, and concluded that there is a whole range of aspiration pneumonias from "benign aspiration pneumonia"[10 11] to acute lung abscess.[12] Cases of non-specific suppurative pneumonia form a group of intermediate severity: in some the pneumonic process predominates; in others abscess formation is more conspicuous. This attractive and simple explanation of the aetiology of suppurative pneumonia has much to commend it, and Nicholson's clear description of the clinical and radiological features of the disease has helped to place this hitherto obscure disorder in its right perspective among the pneumonias.

1 *Guy's Hosp. Rep.*, 1945, **94**, 115.
2 Ibid., 1946, **95**, 40.
3 *Surgery*, 1938, **4**, 728.
4 *J. thorac. Surg.*, 1940, **9**, 439.
5 Ibid., 1942, **12**, 98.
6 *Proc. R. Soc. Med.*, 1938, **31**, 1259.
7 *Thorax*, 1946, **1**, 146.
8 Ibid., 1949, **4**, 125.
9 *Lancet*, 1950, **2**, 549 and 605.
10 Ramsay, H., and Scadding, J. G., *Quart. J. Med.*, 1939, **8**, 79.
11 Scadding, J. G., *Lancet*, 1948, **1**, 89.
12 Brock, R. C., *Guy's Hosp. Rep.*, 1947, **96**, 97, 125, 141.

VIOMYCIN

A series of nine papers in the *American Review of Tuberculosis* for January (1951, **63**, 1–61) is concerned with viomycin, the latest antibiotic to emerge to the point of clinical trial from the wholesale soil-screening programmes now being pursued in the U.S.A. It has been isolated independently in the laboratories of Chas. Pfizer and Co., who have named the organism yielding it *Streptomyces puniceus* on account of the purplish-red colour of its colony, and in those of Parke Davis and Co., whose organism has been named *Streptomyces floridae*, presumably from its origin. It appears to be agreed that the two antibiotics are identical, although the identity of the cultures yielding them—not, of course, a necessary corollary—has not been proved. Viomycin is a strong organic base forming salts which are more or less neutral and freely water-soluble: the sulphate is the most suitable salt for therapeutic use. The striking feature of its antibacterial "spectrum" is its proportionately high activity against *Mycobacteria*, including tubercle bacilli. Many antibiotics possess activity against *Mycobacteria* which is equivalent to that against other bacterial genera, or of a lower order: viomycin appears to be unique in that its action on tubercle bacilli is its outstanding property, most other pathogenic organisms being relatively resistant. Thus concentrations between 1 and 5 μg./ml. suffice to inhibit the growth of most strains of *Myco. tuberculosis*, whereas those required to inhibit that of such organisms as streptococci, staphylococci, pneumococci.

and a number of Gram-negative bacilli are variously stated as 40–80 or over 100 μg./ml. It is quite clear that streptomycin-resistant strains of tubercle bacilli have a normal sensitivity to viomycin. Animal therapeutic tests give corresponding results, except that there is some action *in vivo*, quite unexpected in view of the *in vitro* findings, against three species of Gram-negative bacilli. The drug is well tolerated by animals, and when given in adequate doses has a suppressive effect on tuberculosis in guinea-pigs and mice comparable to that of streptomycin. In these experiments it was administered by injection, but it is known also to be effective when given by the mouth.

So far these findings are very promising, but others are less favourable. Tubercle bacilli habituated to viomycin *in vitro* can acquire a high degree of resistance: the process is rather more gradual than with streptomycin but is nevertheless of the "streptomycin" rather than the "penicillin" type. Preliminary clinical studies have produced a miscellaneous crop of toxic effects which cannot altogether be discounted by the fact that the cases chosen were of a highly unfavourable type. They were 10 patients with far advanced pulmonary disease in most of whom previous chemotherapy had failed. Nine developed albuminuria, two vestibular disturbance and partial deafness, two eosinophilia and urticaria, while five had a serious disturbance of electrolyte balance involving falls in the serum calcium, potassium, phosphorus, and chlorides, with a rise in the carbon-dioxide-combining power, and resulting in anorexia, weakness, lassitude, paraesthesiae, cramps, and, in two patients, frank tetany. The mechanism of these changes could not be determined, but abnormal loss of electrolytes in the urine was judged to be a major factor, and the administration of calcium and potassium salts afforded some relief. The sensitivity of the patient's tubercle bacilli diminished substantially during treatment in five cases, and underwent little or no change in three others: in two the sputum became negative. Such patients were naturally not regarded as material on which to form a judgment of the usefulness of viomycin in treating tuberculosis: this can be determined only by treating less advanced cases. The authors of this study, while decidedly guarded in their conclusions, seem prepared to pursue the matter further. Streptomycin remains emphatically the first choice for the chemotherapy of tuberculosis, but something is still needed for cases with streptomycin-resistant bacilli, and viomycin, despite its drawbacks, is evidently a serious entrant in this subsidiary field.

ANTIBIOTIC TREATMENT OF BACTERIAL ENDOCARDITIS

Bacterial endocarditis is still a formidable disease, despite the success of modern antibiotics. By far the best antibacterial agent is penicillin, and it is now the usual practice to give 1 million units daily for six weeks as a routine. If the infection does not appear to be controlled the daily dose is increased boldly. There are three chief obstacles to successful treatment: the high mortality from heart failure (about 20%), usually at a time when the war against the bacterial enemy has been won; penicillin-resistant bacteria; and complications such as hemiplegia, acute nephritis, cardiac infarction, gross valve damage, and side-effects of therapy that may detract greatly from the successful control of infection. In the opening pages of this issue Dr. J. E. Cates, Professor R. V. Christie, and Professor L. P. Garrod describe four cases of bacterial endocarditis caused by penicillin-resistant organisms, in three of which the infection was controlled by means of large doses of penicillin (20 million units daily) combined with streptomycin (4 g. daily) for a period of at least six weeks. Clinical response was prompt in the fourth case, but death from heart failure supervened before the infection had been entirely eliminated. One of the other patients also died from heart failure 17 days after the antibiotics were discontinued. The two survivors suffered from extensive vestibular damage, with consequent difficulty in walking, and one had early heart failure. Thus, although life was saved, at least temporarily, in two out of four cases, the treatment can hardly be regarded as successful, as anyone who has had to care for patients whose vestibular mechanism has suffered permanently from the devastating effects of toxic doses of streptomycin will appreciate. Experimental work on the pathological changes found in guinea-pigs after the administration of streptomycin was reviewed in an annotation in last week's *Journal*. According to Bignall, Crofton, and Thomas[1] giddiness develops in 60% of patients treated with 2 g. of streptomycin daily, and they were unable to show that antihistamine drugs significantly altered this incidence. Doses of 3 or 4 g. daily for several weeks are likely to cause permanent loss of balance in the majority of cases.

[1] *British Medical Journal*, 1951, 1, 554.

"FAMILY DOCTOR"

Few new magazines have been produced without a hitch, and one hitch usually leads to another. *Family Doctor* has been no exception. Some necessary last-minute readjustments of its contents narrowed the margin of time for printing, and on top of this the printer had his own unforeseen difficulties to contend with. If the public's curiosity about *Family Doctor* had been less acute these birth-pangs would have passed unnoticed by the world outside B.M.A. House. But along with these normal complications of a new production came a demand to see the baby that was as embarrassing as it was flattering. During the last few days before publication orders for copies could not be met, in spite of the fact that the number to be printed had been raised to close on a quarter of a million. As a result of all this there was some difficulty in matching the rate of printing with the pressure of the demand, and some inevitable unevenness of distribution, with consequent disappointment to wholesaler, retailer, and customer. Much of this was made good during the earlier part of this week, and plans have been laid for obtaining even and wide distribution of *Family Doctor* on April 27, the date of publication of the May issue.

Of the magazine itself the most encouraging note in the first number was this observation by Lord Horder: "I hope I may be forgiven a personal note if I say that this magazine is what I have been waiting for—for quite a long time." And it seems, too, it is what the public has been waiting for. The first article for the current issue is on the work of the National Playing Fields Association, prefaced by a message from the Duke of Edinburgh in which he welcomes the support given by the B.M.A. "in its new monthly health magazine, written for the young of all ages." Prince Philip has struck the keynote of this new periodical. What he says is reinforced by the Minister of Health, Mr. Hilary Marquand, when he told a representative gathering of the Press last week that he was "very glad indeed that this new journal has been established." "We must," said Mr. Marquand, "act together, using all our powers to educate the people in the necessity for health, and to encourage them to co-operate with the services of the general practitioner in the maintenance of health." It is the general practitioner who before all others in the N.H.S. sees the early departures from health in the families he looks after as the family doctor. For this reason alone it is hoped that the link between the general practitioner and this new health magazine will be close. Among a good batch of articles in the April issue it is not invidious to pick out as one of the best that by a country G.P. under the title "Patients I Like." This is the kind of article that should do good by letting the public as patient peep over the doctor's garden wall and get some idea of how he looks at life.

HISTORY OF CHOLERA IN EGYPT

The sudden appearance of cholera in Egypt in 1947 after an interval of 45 years was an epidemiological surprise. The first epidemic of cholera recorded in Egypt was in July, 1831, when infection was brought back by pilgrims from Mecca. Although the epidemic began in Cairo it quickly spread over the whole country: 150,000 persons are said to have died—a death rate of 50 per 1,000 of the population. Cholera again appeared in Egypt in 1834, 1837, and 1848, when it broke out in Tantah during the fair, having been imported this time from Constantinople and Asia Minor. Pilgrims returning from the Hedjaz were again responsible for importation of the disease in 1850, 1855, and 1865. In the last of these years 30,000 out of the 90,000 pilgrims who visited Mecca are reported to have died, and in addition Upper Egypt became infected, first at Beni Sueif and later south of Assuan, whence infection spread to Kassala in the Sudan and finally to Abyssinia. The appearance of cholera in Egypt in the summer of 1866 was probably not a reimportation. For the next 18 years Egypt was exempt from infection. Then in June, 1883, it broke out in full fury at Damietta in the Delta during the holding of a fair. Abdel Gawad Hussein,[1] who has collected all the available information on this epidemic, believes that pilgrims who returned from Mecca in October, 1882, were responsible for the importation of the disease, which took just one month to reach Beni Sueif Province in Upper Egypt. Some 58,511 deaths from cholera occurred in Egypt, and, while working in Alexandria, Robert Koch discovered the *Vibrio cholerae*. Raphael Borg, a British consul in Egypt, devoted much research to the epidemiology of cholera during this outbreak. Workers in the copper industry were almost exempt from infection, and among the 25,907 Copts living in Cairo only 170 died. For another 12 years Egypt remained free from infection. Then in the autumn of 1895 it again appeared, continuing into 1896. In all, 19,370 cases were reported, with 16,571 deaths. The source of infection was uncertain, but since cholera was present at Mecca and as far north as el Akaba it is probable that the source of infection was either returning pilgrims or Bedouins from the Sinai peninsula. Seven years later the same story was repeated, pilgrims returning from Mecca causing infection in Assiut province. Although exposed to infection during the years of the first world war Egypt had no epidemic, despite the fact that a single case did occur in 1916 in Port Said in a person recently arrived from India.

On September 22, 1947, cholera suddenly broke out in the village of Korain, Sharkia Province, in Lower Egypt. In Korain the outbreak was explosive, 158 cases with 63 deaths being notified within a week. Within 24 hours of the first case having been reported others were seen at Zagazig, Tel el Kebir, and villages in the Khanka sanitary district. The first case was notified in Ismailia some time later. The total number of cases recorded during the whole outbreak was 20,806, with 10,277 deaths—a death rate of 0.53 per 1,000 of the population as compared with 3.3 per 1,000 in 1896 and 1.7 in 1902. The source of the infection still remains a mystery, for practically at the same time cholera was discovered over a wide area between Cairo and Abou Sueir, a distance of 132 kilometres. Although cholera was prevalent at the time in Pakistan and many British Servicemen were transferred from India to Egypt by air, cholera did not break out in the Canal Zone but in areas where no British were stationed. It is probable that few epidemics of this disease have been studied so intensively as this last Egyptian outbreak. Nation-wide inoculation against cholera was carried out, but only a few figures are available to demonstrate its efficacy. In patients admitted to the Abbassia Fever Hospital, however, the case mortality rate among the unimmunized was 17.3% and among those who had been inoculated 7.6%.

[1] *Med. Pr. Egypt*, 1949, **60**, 627.

The Council of the B.M.A. at its meeting on March 14 unanimously decided to award the Gold Medal of the Association to Dr. E. A. Gregg in recognition of his distinguished services to the Association and to the profession. Dr. Gregg, who succeeded Dr. H. Guy Dain as Chairman of Council in 1949, had previously been chairman of the Insurance Acts Committee and of the Representative Body.

Dr. W. Russell Brain was re-elected President of the Royal College of Physicians of London on March 19. Dr. Russell Brain was first elected President of the College on April 3, 1950.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

WHOOPING-COUGH

BY

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Whooping-cough is the most serious and fatal of the infectious diseases of infancy in this country, with the single exception of infantile gastro-enteritis. Almost two-thirds of the deaths occur in children under the age of 1 year, and of these more than half take place in the first six months. In the past ten years deaths have varied between 700 and 2,400 a year, and they generally exceed those of scarlet fever, diphtheria, and measles put together. The respiratory and possibly the nervous sequelae of whooping-cough still lead to long periods of invalidism.

Season and Age Incidence

Although the disease is more common in winter and spring, it is usually present throughout the year; and between epidemics, unlike measles, it rarely subsides to a very low level. The susceptibility of newborn infants to whooping-cough must be stressed. It has been estimated that not more than 25% of infants are born with circulating antibodies, that these disappear within a few months, and that they seldom or never give full immunity. In some infants under the age of 3 months the disease is mild, but many have dangerous cyanotic and even apnoeic attacks during a paroxysm, and these may be fatal from asphyxia or lead to anoxaemic convulsions. About 65% of children have whooping-cough before entering school.

In older children and adults an attack may be atypical and difficult to diagnose; owing to the size of the larynx they do not whoop. Immunity is not necessarily permanent and second attacks occur, usually in adult life and occasionally in the parents or grandparents of children with whooping-cough.

Pathology

In its earlier stages whooping-cough is a superficial infection of the tracheal and bronchial mucous membrane with the small bacillus *Haemophilus pertussis*. In a few, mostly mild, cases the causal organism is an allied bacillus *H. parapertussis*.

A characteristic result of the infection is the formation of tough bronchial mucus. About the third week of the disease this mucus may be so viscid that it cannot be removed by the action of the cilia. It blocks some of the smaller bronchioles and so may cause collapse of small portions of the lung, with dilatation of the bronchiole above the block and compensatory emphysema of surrounding lung tissue. These small collapsed areas are usually situated in the base of one or both lower lobes. In some cases they involve complete segments of the lower lobes and of the middle lobe (right) and the lingual process (left), and may even involve the whole of one or more of these lobes (Figs. 1, 2, 3, and 4). While this collapse process is taking place the deeper layers of the bronchial walls become infiltrated with lymphocytes, and secondary infection may supervene, giving rise to infected collapse and bronchopneumonia. Bronchopneumonia in whooping-cough is nearly always associated with pulmonary collapse.

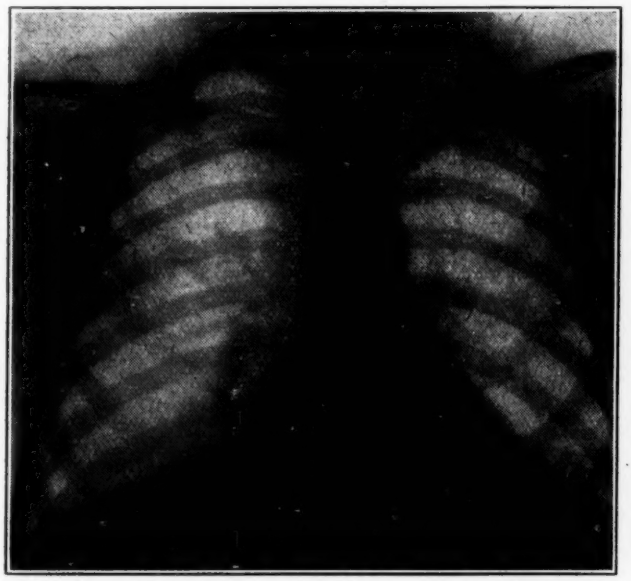

FIG. 1.—Girl aged 5¼ years: 47th day of whooping-cough; ambulant; afebrile except for an occasional "spike" of temperature; respirations 24 to 28. Both cardiophrenic angles in the film are filled with dense shadow, indicating collapse in segments of both lower lobes. A lateral view showed some collapse also in the right middle lobe.

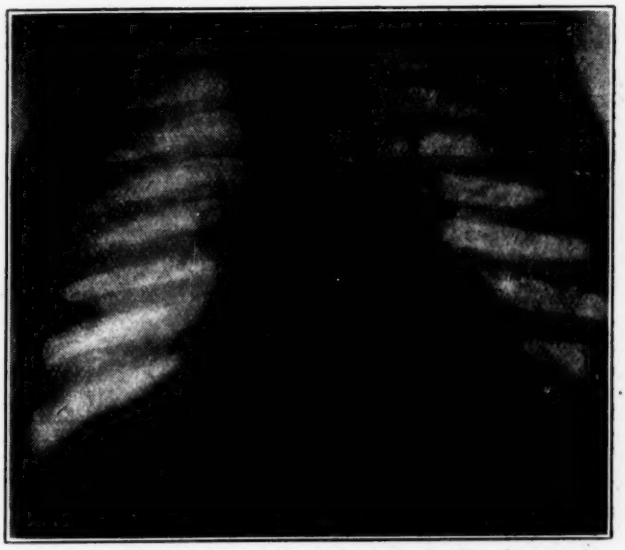

FIG. 2.—Boy aged 1½ years: 30th day of whooping-cough; afebrile when film taken, but with subsequent bouts of pyrexia; respirations 36 to 42. The right cardiophrenic angle (left side of picture) is filled with shadow, denoting segmental collapse in the right lower lobe. The left cardiophrenic angle is not clear-cut, suggesting small areas of collapse in the left lower lobe.

In the ordinary "uncomplicated" case of whooping-cough this process is of course minimal, but small areas of pulmonary collapse are commonly present even in ambulant and afebrile children with severe paroxysms after four to five weeks (Figs. 1 and 2). Perihilar and paratracheal glands may be moderately enlarged in whooping-cough, but not sufficiently to cause pulmonary collapse from external pressure on the bronchi.

The nervous system may be profoundly affected, though there are seldom any gross pathological changes. Minute scattered cerebral haemorrhages due to the mechanical strain of coughing are probably common, but usually symptomless. Occasionally they may be the cause of transient monoplegia, hemiplegia, or paraplegia. Haemorrhages are not the cause of convulsions in whooping-cough and are very rarely fatal; I have only

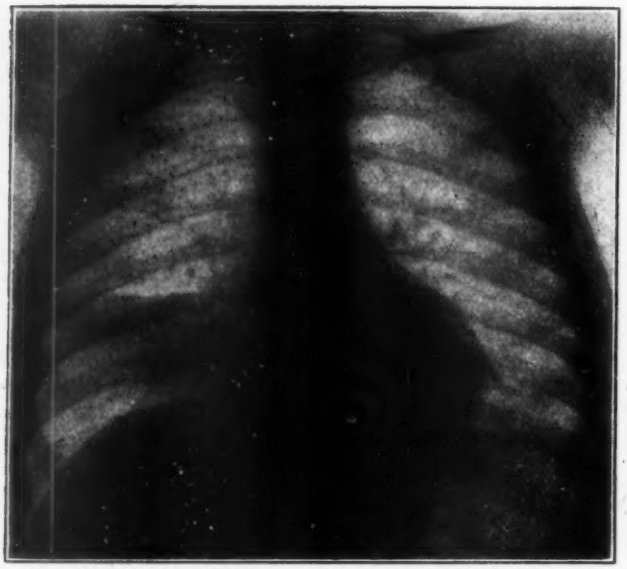

FIG. 3.—Girl aged 3 years: 26th day of whooping-cough; ambulant and afebrile except for occasional evening temperature of 99° F. (37.2° C.). The film shows right middle lobe collapse and also small shadows in the right cardiophrenic angle, suggesting some collapse in the right lower lobe.

once encountered death from cerebral haemorrhage. In patients dying of convulsions little is found in the nervous system beyond congestion and oedema. True encephalitis associated with whooping-cough is quite a rarity, but it may occur suddenly even in a mild case and leave serious sequelae.

Clinical Course

The average case gives little trouble until two to three weeks after onset of the cough, when severe paroxysms with vomiting may lead to loss of sleep, weight, and energy. Pulmonary collapse may begin about this time, especially in children under 5 years of age. The collapsed areas tend to become secondarily infected; the child then gets listless, the respiration rate increases, a cyanotic tinge may appear in the lips, and, if the temperature is taken night and morning, occasional "spikes" of pyrexia will be found. This condition may merge into bronchopneumonia, or bronchopneumonia may start suddenly from the second week onwards. On the other hand, mild and even abortive forms occur, especially in older children and adults and after immunization. Paroxysmal sneezing may partly replace the cough.

Complications

Bronchopneumonia is due to secondary infection with pneumococci, streptococci, staphylococci, or the influenza bacillus. During the past winter highly fatal cases of *H. influenzae* septicaemia have been occurring, associated with intractable bronchopneumonia and convulsions. *Convulsions* are probably the most common immediate cause of death. They are usually associated

FIG. 4.—Same case as in Fig. 3, same day. Right lateral view clearly showing collapse of right middle lobe and of the middle basic segment of the right lower lobe. The left posterior basic segment also seems to be collapsed.

with extensive bronchopneumonia and pulmonary collapse, especially in those cases which show poor or delayed response to antibiotic treatment.

Bronchiectasis is the sequela most to be feared. It is a potential risk in all cases in which pulmonary collapse is present. Many cases of bronchiectasis in schoolchildren have been traced to an attack of whooping-cough some years previously. Fortunately most cases of pulmonary collapse in whooping-cough clear up quite satisfactorily. The child who has a persistent cough for many weeks or months, who is subject to frequent recurrent respiratory acute infections, and who fails to thrive and become lively and active, should without delay be examined for pulmonary collapse and incipient bronchiectasis. The coexistence of measles and whooping-cough, both in the acute stage, is particularly apt to lead to these respiratory troubles.

The danger of *tuberculosis* following whooping-cough has been exaggerated in the past. The coexistence of whooping-cough with a primary complex may, however, be serious, especially in children under 2 years of age. This is the combination which produces occasional cases of acute miliary tuberculosis, with or without meningitis, and, perhaps more rarely, bronchial tuberculosis.

Haemorrhages resulting from the mechanical strain of coughing are rarely serious. The commonest is subconjunctival haemorrhage. Retinal haemorrhage is usually symptomless, but detachment of the retina has occurred. Cerebral haemorrhage has already been mentioned.

Hernia and *prolapse of the rectum* may occur in infants. The latter should be gently reduced each time without any lubricant. It seldom gives trouble after the cough subsides.

Nervous sequelae are just beginning to be recognized. They seem to occur particularly in cases which have recovered after exhibiting convulsions in the acute stage. Follow-up studies suggest that convulsions in subsequent illnesses, ataxia, optic atrophy, petit-mal seizures, and mental retardation may all be sequelae. Retrospective studies of the history of mentally defective schoolchildren have suggested whooping-cough as the starting point in certain instances, but this requires much further investigation.

Diagnosis

In a typical case the diagnosis is usually easily made on the history of a dry cough steadily developing and becoming paroxysmal, especially if there is a history of contact with a definite case, if the cough is worse at night, if sputum is coughed up and not swallowed, if the cough is followed by vomiting, if the child's face goes red in a paroxysm, or if there is ulceration of the fraenum of the tongue. But many attacks are mild and atypical, and laboratory tests are not yet 100% reliable.

In most cases, however, *H. pertussis* can be cultivated during the first three weeks of the disease: (1) by holding a fresh plate of Bordet's culture medium about 3 in. (7.5 cm.) from the patient's mouth during a paroxysm (cough plate method); and (2) by passing a fine pernasal swab along the floor of the nose to the nasopharynx just after a paroxysm (pernasal swab method). For these tests it is usually necessary to induce a paroxysm. To do this, place the thumb in the child's suprasternal notch, with the other hand extend the head *fully* and then flex it sharply, thus allowing the thumb to ride lightly over the child's trachea. If the child has not coughed for an hour or two this manœuvre is usually immediately successful. The paroxysm so induced will generally make the diagnosis clear, but it may be confirmed, in some cases at least, by the use of the pernasal swab, which can be conveniently carried about. Unfortunately, a report may not be received for three to five days owing to the slow growth and small colonies of *H. pertussis*.

A blood count will almost invariably show a well-marked relative and absolute lymphocytosis by the second week of the disease, and often in the first week.

General Management

The average patient, who is virtually apyrexial, should not be left in bed. In good weather he should certainly be out of doors. The difficulty is the management of these cases in winter and during bad weather. Many can brave the elements with benefit. Others must be kept for weeks at a relatively uniform temperature indoors. It is essential to avoid so far as is possible secondary acute respiratory infections, and especially measles. All children should be encouraged to sit up during a paroxysm, should be supported, allowed to whoop as loud as they like, and trained to use a basin for expectoration and vomit. Their lips should be wiped with damp swabs or tissue paper and these latter should preferably be burned.

Temperatures should be taken night and morning if there is the least suspicion that the child is not going on well. After the second week, occasional evening pyrexia, slightly raised respirations, cyanosis of the lips, and listlessness are suspicious signs demanding careful examination, including usually an *x*-ray film of the chest. This may entail sending the child by ambulance or private transport to an infectious diseases hospital. If bronchopneumonia develops, hospital treatment will often be required, for in whooping-cough it is a major illness.

If newborn infants contract the infection (a happening which should always be prevented if possible), and if they are threatened with apnoeic attacks in a paroxysm, it is desirable to send them to hospital with their mothers so that they can be breast-fed.

Treatment of Symptoms

There is no drug treatment which consistently produces dramatic improvement in whooping-cough. We can only hope to modify the course of the disease and prevent serious complications. This is more easily done in summer than in winter, when so many adverse factors such as cold damp weather, upper respiratory infections, influenza, measles, or pneumonia interfere with the action of a remedy, and lead to a return of coughing and vomiting.

Antispasmodics and Sedatives.—Bromoform drops, one for each year of age up to 6, or elixir bromoformi, ½ to 2 dr. (1.75 to 7 ml.), or sodium bromide, codeine, or phenobarbitone are commonly used as sedatives. Ephedrine, ¼ to ½ gr. (16 to 32 mg.) twice daily for an infant, and tincture of stramonium or of belladonna, 5 to 15 min. (0.3 to 0.9 ml.), have been much used in an attempt to relax spasm of the bronchial muscle. In small doses these drugs may do little more than irritate the stomach and may actually increase vomiting. Toxic doses will damp down the cough, but this degree of sedation is harmful. By reducing the force of the paroxysms these drugs may encourage the retention of mucus and pulmonary collapse. It is difficult to steer a middle course, and before prescribing such drugs each case should be considered on its merits. Phenobarbitone is probably as good a sedative as any, but it should not be prescribed in the presence of persistent cyanosis, or signs of pulmonary collapse or bronchopneumonia. In infants it may be given in doses of ¼ gr. (8 mg.) thrice daily. Elixir of luminal (¼ gr. in one teaspoonful) is a convenient preparation. Atropine methylnitrate ("eumydrin"), which is used for dilating the pyloric sphincter in pyloric stenosis, can also be given as a sedative in 0.6% alcoholic solution, four to eight drops four-hourly. It has the advantage of not increasing vomiting and may sometimes relieve it.

Expectorants.—Ipecacuanha, ammonium carbonate, potassium iodide, and large doses of alkaline mixture for the older patients are all employed in what is often a vain endeavour to thin or dissolve the bronchial mucus. These drugs increase salivation and may induce vomiting. They are occasionally useful from the fourth week onwards, when the mucus is very viscid, but should not be prescribed as a routine or for long periods. They are hardly at all used in hospital.

The Decompression Chamber.—This treatment is the equivalent of an aeroplane flight at 12,000 feet for 45

minutes. It is suitable only for uncomplicated cases after the third week of the disease as an aid to clearing up severe paroxysms and stopping vomiting. It is contraindicated in pyrexial or pneumonic cases or those with cyanosis, but not in apyrexial cases with limited pulmonary collapse. It is being used experimentally at Park Hospital, London, and particulars can be obtained from the Emergency Bed Service.

Specific Treatment

Pertussis Vaccines.—I know of no convincing evidence that vaccines have any appreciable effect in the treatment of the ordinary case of whooping-cough in a child. They may have a place, however, as boosters of immunity in cases contracting whooping-cough after previous immunization, and possibly also in adults, as the latter are likely to possess some degree of basal immunity.

Chloramphenicol.—This is probably the best specific drug for whooping-cough, but its action is rarely dramatic. During the past winter, indeed, it has often proved disappointing. It is a very expensive drug and should not be wasted on mild or late cases or where an inadequate course is likely to be given. It should be given preferably before the twelfth day of the disease and only in cases which appear to be developing severe paroxysms. Subject to this, the earlier it is given the better. Usually some improvement in the cough is apparent about the fifth or sixth day of treatment. In ordinary dosage it does not kill but merely inhibits *H. pertussis*, and consequently a relapse may occur if the course is terminated much before the twenty-first day of disease. As a rule a ten-day course is indicated or, alternatively, a seven-day course followed by one of five days after a few days' interval. In children of 1 to 4 years administration is not easy owing to the bitter taste of the drug. Infants under 3 months are usually suitable cases for this drug unless the attack is very mild. Dosage is still uncertain. At present the following is suggested: four capsules (1 g.) a day for infants under 1 year; six capsules from age 1 to 3 years; and eight capsules daily from 3 to 10 years. These amounts should be given in divided doses at six- to eight-hour intervals. In hospital the nurses have little difficulty in giving the drug: they prefer the powder to be disguised in a sweetened or flavoured watery vehicle rather than a syrupy one. The child's nose may be gently held if necessary and the draught is then rapidly swallowed.

Treatment of Complications

For *bronchopneumonia* peniciilin is indicated in high dosage, ranging from 100,000 units three-hourly to 500,000 units four-hourly. Severe cases may require to be admitted to hospital owing to the difficulty of treatment and the danger of convulsions. The oxygen tent should be employed wherever possible, and chloramphenicol may be required in addition to penicillin in resistant cases.

Convulsions are treated with soluble phenobarbitone intramuscularly or paraldehyde rectally or intramuscularly, but often with disappointing results.

Pulmonary Collapse.—If afebrile, the child should be up and about. Milder cases often clear up without special treatment. Resistant cases should be under the supervision of a specialist. Postural drainage should be encouraged over a Brompton frame, or equivalent double inclined plane, with the head downwards and 12 to 18 in. (30–45 cm.) below the level of the buttocks Bronchoscopy may be required.

Prevention

Isolation.—A child with whooping-cough should be isolated so far as is possible from young children and especially from infants for at least the first five weeks of the disease. *H. pertussis* is not often cultivated from the bronchial secretions after three weeks from onset of the cough and hardly ever after five weeks The duration of infectivity is therefore believed to extend to five weeks at the outside, even though the child may continue to have paroxysms of coughing and vomiting for six to ten weeks or more It would seem that after the third week it is secondary infection which is mainly responsible for keeping up the bronchial irritation and the secretion of bronchial mucus that sets up the spasmodic cough reflex. There are many instances in which paroxysmal coughing and vomiting, after they have virtually ceased, are restarted by a fresh "cold" or other respiratory infection.

A newborn child should never be allowed to come into contact with any sibling or other person suffering from whooping-cough if it can possibly be avoided. Before the child is born or brought into such a household. the affected children should be sent away to hospital or elsewhere. This should be a routine precaution in the management of the puerperium.

While it may often be impossible to isolate a child with whooping-cough in a family of three or more children, the objective should be, if possible, to postpone whooping-cough till after 3 years of age. Return of the uncomplicated case to school may be considered safe after the fifth week from onset, but where paroxysms are still frequent or violent return to school may be delayed.

Immunization.—Pertussis vaccines for prophylaxis alone or combined with diphtheria A.P.T. have been the subject of extensive trials by the Medical Research Council in the last three years. The results will shortly be published. It is known that the incidence and severity of whooping-cough in the inoculated cases in these trials were appreciably less than in the controls, but that there was considerable variation in the results as between one vaccine and another, and even between different batches of the same vaccine. The best results were obtained with a vaccine not made commercially Unfortunately it is much easier to make a bad pertussis vaccine than a good one. Until the processing has been improved there will inevitably be some disappointment in the results of whooping-cough immunization. But if whooping-cough is contracted within two years or so of immunization it will often be mild, and in some cases the attack will be prevented altogether or postponed to a less dangerous age. Immunization may be attempted at any time after the age of 2 months, but, as in diphtheria immunization, the earlier it is done the greater the need for an early boosting dose. A "booster" should be given after an interval of six to twelve months if immunization has been done within the first year of life. It is well to get immunizations over before the end of May in districts where poliomyelitis may occur. Whenever signs of epidemic prevalence of poliomyelitis appear, immunization against whooping-cough should at once be suspended until the incidence of poliomyelitis has fallen to a low level—that is, generally until the end of the year. Combined pertussis vaccine and A.P.T. should, in these circumstances, be particularly avoided.

MENTAL HEALTH AND THE COMMUNITY

The National Association for Mental Health organized a joint conference of clinical workers and administrators on March 12 and 13 to consider "Community Mental Health in Practice." After an opening session, which was addressed by several speakers, the Conference split up into discussion groups charged with considering the child and the family, the adolescent and his school, the adult and industry, and the aged in the community. Later at a plenary meeting the groups gave the results of their further explorations.

Milestones in Psychological Medicine

The conference was opened by Dr. W. RUSSELL BRAIN, P.R.C.P., who traced the developments in psychological medicine which had taken place within his own experience. Many of Freud's views, he said, had been rightly criticized, but Freud did make two great contributions—one that unconscious factors influenced the mind, and the other, even more important, that doctors could influence the minds of their patients therapeutically by psychological methods. The next great discovery in psychiatry was in the 'twenties, when the electrical rhythms of the brain were demonstrated, and it was shown to be possible to base diagnosis on abnormality of rhythm. Then followed the use of insulin and electrical shock in the treatment of mental disorder, and, most revolutionary of all, leucotomy, with its possibilities for altering the personality. These developments, said Dr. Brain, brought into sharp relief the tremendous responsibility which devolved upon the psychiatrist. He was convinced that these physical approaches in no way precluded or made invalid the psychological approach. The two were not mutually exclusive, and he made a strong plea for respect for the personality of the individual, however much that personality might be undeveloped or deformed by disease.

Social Indices of Maladaptation

Dr. ROBERT SUTHERLAND, late medical adviser and secretary of the Central Council for Health Education, who presided, spoke of the prevalence of mental ills in the community. Delinquency, which was only a partial index, might be regarded as a demonstration of the failure of society to meet the needs of young people in certain social conditions. In 1948—the most recent year for which figures were available—there was one divorce or separation for every nine marriages; an extremely challenging figure. In the same year there were 4,700 suicides in this country, each of them a confession of defeat by the individual; and 300 cases of murder or infanticide, each representing the ultimate protest of the individual against society. Many other indices might be taken, but these sprang to the mind. It was computed that one out of every three people who went to the doctor was not suffering from any organic disease. These were cases of disturbed personality and of emotional wear and tear; not mental disorder in the grave sense, but a disturbance of mental health which made the people feel ill.

Emotional stress, continued for months and years, was an important factor in most diseases. But why did some people manage to make a reasonable adjustment? There must be something in certain individuals which caused them to react in a highly sensitized way. The preventive aspects of mental health must not be overlooked. It was evident that in the search for the fundamental causes of mental disturbances and their rectification there was an immense field to cover.

Dr. T. A. RATCLIFFE, consultant neuro-psychiatrist of the Ministry of Pensions in the Nottingham Region, said that legislation had always laid its principal stress on the improvement of material factors. Only gradually had aspects other than the purely material been introduced, and even the most recent social legislation was heavily weighted towards the material side. The attitude towards the National Health Service, for example, had been so closely concerned with meeting physical requirements that the importance of the doctor–patient relationship had been largely forgotten, as well as, for that matter, the importance of good professional–administrative relationships. He went on to speak of the many sufferers from mental ill-health who did not fall within the province of the orthodox psychiatric clinic. These were socially maladjusted people, and the question was to what extent this group became the province of the expert in mental health.

Help for the Misfit

The largest single experiment in this field had been the work of the Community Care Service of the National Association for Mental Health. Started as a regional after-care scheme for men invalided from the Forces with psychiatric disability, it had developed into a comprehensive service for community care of social misfits. The team consisted of the psychiatrist and psychiatric and other social workers, but it was the psychiatric social worker who took the major therapeutic role, the psychiatrist remaining as a technical adviser and co-ordinator in the background. The interviews with the patient were an essential part of the treatment process, during which the patient's tensions and difficulties were unravelled.

The process might be described in terms of depth psychology, but Dr. Ratcliffe preferred to consider it simply as "relationship therapy," one common factor in socially maladjusted people being their difficulty in forming stable or satisfactory human relationships with others in their environment. In the community care technique, relationship was slowly built up. It was not a relationship in which the aim was the dependency of the patient on the psychiatric social worker, either in the material or in the emotional sense; it was rather an educative process towards mature independence. In one group, out of 30 men and women with grossly unstable work records 24 had been helped to a worth-while degree and four others to a smaller degree. These were the hopeless failures of more orthodox and established methods.

The local authority, though shorn—as he thought, unfortunately—of much of its responsibility for health services by the Act, had community care of this type still within its province. Here was an opportunity to work up a worth-while service. Some local authorities had accepted the challenge and had begun to build a real community care service. The technique was time-consuming, yet it should be compared in this respect with the wastage of man-hours owing to absenteeism in industry, with the repeated and often fruitless efforts of various social agencies to deal with the problem family, with the overcrowded surgeries, and with the amount of medicines consumed in cases of minor ill-health. A local mental health community care service could be built up if the team of psychiatrist and psychiatric and other social workers were in close collaboration with all the available social services of the area.

Old Age and Social Isolation

Short addresses were given by workers in child-guidance clinics and rehabilitation centres on community care in relation to the child, the adolescent, and the working adult, and Dr. FELIX POST, physician to Bethlem and Maudsley Hospitals, brought up the rear with a talk on the aged. Mental ill-health in old age, he said, was not solely due to some relentlessly progressive process of brain deterioration, but in a large proportion of cases was decisively influenced by unfortunate circumstances in the environment. In many of these people it was possible to bring about, if not recovery, at all events great improvement, but this was often only the beginning of the struggle against relapse. It was clearly desirable to get such patients back into normal community life. Dr. Post hoped that valuable experience had already been gained in applying measures likely to help ageing people by placing them in suitable jobs, by assisting them in the course of social case-work with themselves and their relatives, by bringing them out of positions of isolation, and, in short, by combating influences from the environment which tended to hasten the onset of senility. One wise observation was that relatives, although they might try hard, were often not suitable companions for the discharged geriatric patient.

HEALTH SERVICE ADMINISTRATION

LONDON CONFERENCE

A conference organized by the Institute of Public Administration, with the co-operation of a number of other bodies, including the British Medical Association, the Society of Medical Officers of Health, and the Executive Councils Association, was held at Church House, Westminster, on March 14, 15, and 16, for discussions on some administrative problems of the National Health Service. The delegates from hospital authorities, executive councils, and local health administrations numbered some 400, and there were also present observers from India and Pakistan, the Rockefeller Foundation, and W.H.O.

The chair was taken by Mr. HENRY LESSER, chairman of the London Executive Council, who reminded the conference of the vast uncoordinated health services which had had to be brought within the framework of the one scheme. Every branch was prone to look on its problems in isolation. Was there enough of the team spirit among those who were serving under the present tripartite arrangement to make the Service "go," or did such experience as had already been gained point to the need for some kind of co-ordinating machinery which would reduce the risk of friction or frustration?

The General Practitioner

The first discussion was on the administrative problems of the general practitioner. The opening paper was given by Dr. A. TALBOT ROGERS, chairman of the Kent and Canterbury Local Medical Committee, who reviewed the history of National Health Insurance and the transition to the new Service. He pointed out the extent to which the National Health Service had followed on the lines of the earlier insurance scheme, with similar administrative units under new names and with wider responsibilities. Two administrative innovations were the Medical Practices Committee and the Tribunal. Of local medical committees he said that these bodies, in the tradition of the old panel committees, could justly claim their share of credit for the hard work that had gone to solving many of the new problems arising under the Act. He urged a more general representation of the local medical profession on the health committee of the local authority and more general-practitioner participation in committee work at all administrative levels in the hospital field.

A host of questions, said Dr. Rogers, awaited solution. Foremost among them was the adequacy of general-practitioner remuneration and its method of distribution, but they also included the size of the permitted list, the safeguarding of general-practitioner status, faults arising under the trainee-assistant scheme, the need for an easier mode of entrance into practice for the newly qualified doctor, and the provision of extra help for tuberculous cases, the chronic sick, and the aged infirm.

Was enough being done to safeguard the status of the general practitioner and to allow him to continue to do satisfying work and to have adequate ancillary assistance? The life of the general practitioner was not now as satisfying as formerly—a difference not wholly attributable to the Health Service Act—because of the change in the relationship with his patient. It was possible that the length of the permitted list would have to be looked at again. A man with a list of 4,000 suffered some discontent because the extra load of work made it necessary for him to alter some of his methods and to work under greater time stress.

Dr. W. E. DORNAN, chairman of the Medical Practices Committee, gave some account of the work and functions of that body. It consisted of seven doctors and two lay members, the doctor members being drawn from various parts of the country and representing different types of practice. If some people had their way most of England and Wales would be a closed area, so that it was as well that there should be a statutory committee charged with the duty of determining whether an area should be closed or not. In his view there should be as little interference as possible. A doctor should be able to practise wherever he desired, so far as this was compatible with the public interest.

Dr. D. F. HUTCHINSON, secretary of the Middlesex Local Medical Committee, said that as a whole general practitioners were not happy in the Service. They were not satisfied that the Service as at present administered enabled them to do the best possible for their patients. One of the most essential things was co-operation between the three parts of the Service. In some areas there was not sufficient opportunity for the general-practitioner point of view to be placed before the hospital authorities, the executive councils, and the local health committee. Instead of getting nearer to the hospital service, the general practitioner was being pushed away.

Sir WILLIAM MARSHALL, of the Scottish Association of Executive Councils, said that on the whole the executive councils and local medical committees were putting the right men in the right places, but the young doctor was experiencing great difficulty in getting established. It was a matter of concern that so many men, married and with considerable hospital and general-practice experience, should be applying for one job after another and seem to have little hope of a permanent home. They were men well fitted to be principals, and yet were unable to obtain an assistantship with a view to partnership. Basic salary did not go far to meet expenses of practice, and in any case every grant of basic salary in some degree diminished the emoluments of other doctors in the area.

Dr. HOWIE WOOD (Isle of Wight) spoke as a general practitioner contented, generally speaking, with the Service. He was a member of a group practice before the Act came in, and the principles of the practice had been carried into the new set-up. Remuneration was the chief matter of criticism of the Service by general practitioners. The Minister's promise that remuneration should be fixed had never been implemented. He pleaded for greater use of the trainee-assistant scheme. A former trainee of his was now his partner.

The Doctor in the Hospital

The problem of hospital administration was introduced by Mr. J. CRAWFORD FIELD, secretary of the Southend-on-Sea Hospital, who said that the struggle for power between the secretary and other lay officers of a hospital could lead only to the appointment of another officer to co-ordinate them, and "the prospect that this may be a medical man is very real," medical men being the only men in the Service with the necessary personality and educational background. But one craft in a multi-craft organization should not dominate the others. Moreover, a local medical administrator would mean the by-passing of the hospital management committee. If the secretary became hospital administrator, as he hoped, some sweeter-sounding name than "secretary" should be found for him.

Dr. T. ROWLAND HILL, chairman of the Central Consultants and Specialists Committee of the British Medical Association, said that the comparative smoothness with which the National Health Service came in, and the continuance of the medical work without pause, was really a tribute not so much to the Act itself as to the manner in which the medical profession, with the world changing around it, carried on uninterruptedly under the guidance of its age-old tradition. One defect in the hospital administration was that the principles of junior staffing had not been clearly seen or laid down, with the resulting confusion over the number of registrars and similar officers. He had views as to the wisdom of the change whereby the present method of the mixed lay and medical appointments advisory committees had replaced the old method of medical committees to advise hospital managers on the choice of new consultants. Joint consultation at the highest level should be developed fully,

not merely for medical but for other senior and responsible staffs.

"Adequate joint consultation (by which staffs are made to feel colleagues or partners in a great endeavour) between administrative authorities and senior medical staff is essential to the maintenance of a vigorous, progressive hospital service with powers of spontaneous development. We regard its establishment as the single most important administrative step to be taken in the hospital service as far as medical staff are concerned."

After all, joint consultation between employers and staff was now a generally accepted principle throughout the whole field of employment. In his opinion it had so far been insufficiently developed in the N.H.S. It was, of course, joint consultation at the highest level that was the most important. It must not be assumed that the doctor who went into hospital for the purpose of practising medicine was not interested in administrative problems of hospital life. Hospitals had grown up to what they were to-day by a spirit of partnership between administrators and the members of the medical and other professions who had worked with them, and that spirit—a republican rather than an authoritarian spirit—should continue.

Dr. E. B. BROOKE, medical superintendent of St. Helier's Hospital, said that the real problem which confronted them to-day was the right use of hospital beds. They were sometimes told how many of their hospital beds were filled with the aged chronic sick. But age did not really come into it. Their well-equipped hospitals should be used for the highly specialized purposes for which they were designed, whatever the age of the patient, and any tendency to think twice about the admission of elderly patients on the ground of their years should be frowned upon. The position was that they had too many patients in search of too few beds, and they had to exercise a wise priority to see that they got the right patients. The patient was the only *raison d'être* of hospital administration.

Mr. S. C. HILL, secretary of the Coventry Hospital Management Committee, said that his idea of hospital management was to provide a good hospital service where it was wanted, when it was wanted, and to the extent to which it was wanted. Three years was not long enough for a true assessment of the health services as such.

Miss CHERRY MORRIS, almoner at the National Hospital for Nervous Diseases, opened a discussion on medico-social services, and suggested that it was the middle class who were expressing the warmest gratitude for the National Health Service. These people, many of whom belonged to the professional classes, had previously been only beginning to find their way to the hospitals. They had not been at all sure of their welcome there, and if received they had often been heavily assessed. Now they were thankful to be able to have medical care at home for themselves and their families without running up doctors' bills which they could not afford. Miss Morris also said that while much had been said about the old chronic sick, the young chronic sick—such as the young person with disseminated sclerosis with progressive muscular atrophy—were never mentioned. There was nothing for them. They were too ill to be sent home, yet could not remain in "acute" hospitals; and, as likely as not, if they were put in a chronic sick ward their next neighbour was 80, and not a very bright 80 at that. A gap in the provision under the Health Act would be filled if there were special accommodation for young chronics.

Mental Health Services

On its second day the Conference considered mental health services, opening with a paper by Dr. A. TORRIE, medical director of the National Association for Mental Health. He outlined the provisions of the Act so far as mental health was concerned, and said that the problem was a composite one which called for a combined approach by all Government agencies concerned to see that the right measures were applied by the right people and at the right time. The fact that responsibility for the care of mental patients was now divided between local health authorities and regional hospital boards might mean that the social worker employed by the former under Section 23 of the Act visited a patient before admission to a mental hospital or before treatment at a psychiatric clinic, while the social worker of the hospital or clinic subsequently followed him up. It was obvious that the interests of both the patient and his family would suffer in such an event unless there was the closest co-operation between the two social workers concerned. The best plan would be the joint use of a social worker by the two bodies.

Dr. Torrie, who estimated that one-third of all sickness was due to mental ill-health, said that a large proportion of the £31m. spent on pharmaceutical services could be saved if the right measures to counter mental ill-health were applied again by the right people at the right time. He had been formerly a family doctor and he had learned that the important thing in very many cases was to give not a bottle of medicine but a listening ear. He went on to say that he believed in the Health Act, though he regretted that it was "an Act in a hurry." It was a pity that there had not been a pilot run. The Minister should make it compulsory upon local authorities to afford provision for mental sickness.

Dr. C. KENTON, psychiatrist of the North-west Metropolitan Hospital Board, held that the administration of mental hospitals had been distinguished by economy and efficiency in very favourable comparison with the general hospital groups, and the difference was largely due to the length of experience in hospital work which the administrators in the mental health service had enjoyed. He discussed the question of old people in mental hospitals. One in five of the patients admitted was over 65. This admission rate was in excess of what could reasonably be expected, even allowing for the increased numbers of old people in the general population. The cause was largely the financial incentives to hospitalization and the disinclination of young people to be responsible for elderly relatives needing mental care. Legislative advances towards centralization had done much to loosen family ties.

Dr. FRANK BODMAN, psychiatrist to Somerset County Council, spoke of the preventive value of child-guidance clinics. On paper these clinics numbered something like 200, but many of them were very small affairs, giving only a half-day service twice a week, or some such period, and were not necessarily served by a specialist in child psychiatry.

The Local Health Authority

The Conference then turned to the diminished role of local health authorities—"shorn lambs," as one speaker called them—in the National Health Service. Dr. J. A. SCOTT, deputy medical officer of health, L.C.C. (who stated, however, that the L.C.C. was not responsible for his remarks), enlarged upon the immensity of Mr. Bevan's problem in 1945. Mr. Ernest Brown's previous proposals for a medical service had been rejected point blank by the medical profession; Mr. Willink's White Paper was no more fortunate.

"The doctors said they would not be Civil Servants, and would not be local government officers, and they meant it. Hence, I take it, the necessity for Mr. Bevan's brilliant *tour de force*, with its complete acceptance of the unitary nature of clinical medicine. . . . It is doubtful whether proposals for any other kind of administrative structure would have secured the acquiescence and in due course the co-operation of the doctors; but, however valid the reasons, dividing the Service, like Gaul, into three parts has created administrative problems of varying degrees of magnitude. Insistence on the unity of clinical medicine has fractured various other unities no less real."

The result was that administrative problems in the fields of tuberculosis, maternity, infectious diseases, mental illness, and the chronic sick had needed much liaison work.

Dr. Scott urged that what was wanted essentially was a body capable of taking a comprehensive view of all the problems—general-practitioner, local health authority, and hospital—in each area. For such a tripartite liaison committee the hospital management committee area was too

small and the regional hospital board area too big, though the latter was the more feasible planning unit. Any tripartite committee should be advisory only, its members reporting back to their parent bodies for both information and action. But tripartite committees were a short-term remedy only; the long-term solution to many of these administrative problems probably lay in the overdue reform of local government.

Efforts at Co-ordination

In the discussion following Dr. Scott's remarks many representatives of local authorities spoke of effective liaison which had been achieved in their area. Alderman Mrs. V. F. KING, of the Southampton County Council, said that her progressive authority had co-opted a general practitioner to its health committee, had instituted regular meetings of the committee with the almoners of all the hospitals of the district, and from the appointed day its medical officer of health had had a seat on the local executive council and on the hospital management committee.

Dr. A. ELLIOTT, M.O.H., Kent County Council, who pointed out that many current problems were not the result of the Act but of the economic difficulties of the country, spoke in particular of maternity services. He mentioned that in an excellent residential neighbourhood near London 80% of all confinements took place in hospital, whereas in one of the worst-housed areas this proportion was only 40%. He thought that hospital management committees were too self-contained in respect of maternity accommodation. Admission to beds should be according to need and not governed by the existence of a surplus of beds in one area and a deficiency in another. As to health centres, he doubted whether they would increase much beyond the one which was being built in London and the other in Manchester.

A more pessimistic note was struck by Dr. G. W. H. TOWNSEND, M.O.H., Buckinghamshire County Council. He feared that the separation of the different parts of the Service would tend to increase. The local health authority and the regional hospital board would get further apart, and the setting up of liaison committees was only temporizing with the situation. There should be a system of interchange of officers and members of the respective bodies. It should be a statutory obligation that members of county and county borough councils should be elected in large numbers to hospital boards, instead of putting up a superstructure of liaison committees. The ultimate solution was a larger form of local authority, possibly regional, with all health services under its control. Dr. W. D. CARRUTHERS, M.O.H., Staffordshire County Council, pointed out that at present medical officers of health, who had the responsibility for the notification of infectious diseases, had had sufficient experience of infectious diseases hospitals to discharge this duty with full efficiency, but with the divorce from the hospitals a new generation might find it increasingly difficult to keep themselves up to date.

Dr. J. L. MCCALLUM, general practitioner, of Holborn, said that the London Local Medical Committee, of which he was a member, had lately protested against the admission of normal midwifery cases to hospital when people were dying at home for want of admission. On the other hand, some were of opinion that all maternity work should be institutionalized and under specialist care. The standard of care in London in domiciliary midwifery, thanks especially to the midwives, was extremely high, and he felt that where housing facilities were reasonably good it was psychologically better for the mother to have her baby at home. A compromise might be made by providing under the National Health Service something on the lines of private maternity homes for normal cases, costing perhaps only half that of the occupation of a hospital bed.

Dr. STUART LAIDLAW, M.O.H., Glasgow, speaking of the co-ordination of services, said that one specially charged co-ordinator was better than a committee, "which keeps the minutes and wastes the time." There was excellent liaison in Glasgow between the regional hospitals and the local authority. The link-up in infectious-diseases services was good. There was no doubt that mass-radiography services should be vested in the local authority. Co-ordination had been achieved in respect of all antenatal and post-natal clinics in Glasgow.

The Cost of the Service

The third day of the Conference opened with a discussion on the cost of the Service. Mr. FRANÇOIS LAFITTE, chairman of the P.E.P. Health Group, gave the total net cost for 1950–1 as £451m., of which hospital services absorbed £267m. The general medical services cost £54m. There were no means at present, he said, of estimating the other side of the account—the value of the Service. The essential factor, the effect on the health of citizens, was still unknown.

On the pay of general practitioners Mr. Lafitte thought that doctors with small practices in country and middle-class areas had done less well, while many with large practices in other districts had done much better than was expected.

"Almost all informed persons outside the ranks of the specialists, and a good many within their ranks, believe that specialists as a class—bearing in mind how the State has transformed their circumstances—are overpaid. That is also my opinion. . . . We cannot disregard the eventual harm to the practice of medicine itself that is likely to result from maintaining the present disparities in the rewards of these two groups of doctors. If payments to specialists cannot be scaled down, then for that reason alone I think the State will be driven to increase its payments to general practitioners."

When it came to policy making, Mr. Lafitte's impression was that the weightiest agencies were the hospital authorities, remote from any body of rate or tax payers, controlling great resources, and backed by the prestige of the State. The shape of the medical care and services they were imposing was, he suspected, derived from their own particular attitude to medical care, which was largely that of the specialist clinicians.

"It may well be that we shall have neither 'rational planning' nor economical budgeting until the power to allocate funds between the different branches of the N.H.S. is vested in some authority, below the level of central government, which is competent to look at every aspect of the position in a particular place, and is responsible for finding part of the necessary funds from local, not central, sources."

Mr. W. L. ABERNETHY, assistant comptroller, L.C.C., said that the publicity given in the national press to dentists' remuneration had made an already unpopular profession even more unpopular.

Mr. J. A. SPEED, secretary of the Executive Councils Association, said that the general-practitioner service was the least understood and did the most work. He controverted some points in Mr. Lafitte's remarks. Mr. Lafitte had said that under National Health Insurance a ceiling was set on expenditure on drugs; there was no such ceiling. He had also said that it was hard to believe that it was medically necessary that one-third of all prescriptions should be for proprietary medicaments. Mr. Speed, for his part, wanted to see 90% of medicines proprietary, because with such drugs, thanks to the research departments of the manufacturers, there was likely to be a standard, though he agreed that there were too many brands of the same thing—they did not want 50 brands of aspirin, for example—and proprietary medicines should be cheaper because they were mass-produced.

General Practitioners' Remuneration

Dr. J. L. MCCALLUM drew attention to the fact that in estimating the cost of the general medical service at £54m. for 1950–1 Mr. Lafitte had included £5.7m. for practices compensation, which was mostly for people who had left the Service. With this deduction, general-practitioner services accounted for approximately 10% of the total bill.

but much more than 10% of the service was done by the general practitioner.

Dr. HOWIE WOOD (Isle of Wight) said that at present general practitioners' remuneration was a sore spot, not only as to its adequacy but as to its distribution. More work was also being demanded of the general practitioner. A proportion of it from the medical point of view was very welcome as conducing to the common health, but there were frivolous complaints which could not be justified. Comparing the general practitioner with the dentist and the specialist, he said that this was another sore spot, for the practitioner was on call for the 24 hours. The surgeon, before the Act came in, had also a considerable amount of emergency work, but under the new arrangements he had very seldom to turn out in the middle of the night, because all this work was done by registrars. He was not criticizing the remuneration paid in other branches of the Service, but the general practitioner who had to do more work should be paid adequate remuneration. With regard to the cost of prescriptions, what they did at present, and prided themselves on doing, was to use on occasion as necessary expensive drugs with a view to hastening the recovery of the patient, thereby saving the country a lot of money. Drugs like penicillin and "aureomycin" cost large sums of money, but the use of these preparations meant that many man-hours were saved.

A Lancashire alderman who joined in the discussion considered that only a whole-time State-salaried service could give the practitioner the proper incentive for efficiency. This, he said, would mean a great saving on pharmaceutical services, and practitioners, so far from losing their independence, would be free from deterrents and pressures which at present hindered their best work. He was followed by an Oxford councillor, who protested against big lists. To restore to the general practitioner the opportunity to use his clinical judgment it was necessary to bring down the maximum to 2,500 or 2,000. A dental practitioner, on the question of the dental service, said that in London last year the average payment to dentists was only £1,500 net, after allowing only 52% for expenses, which he thought was too low.

Payment of Specialists

Mr. LAFITTE said that the Spens Committee might have gone on the principle that the average income of specialists from the age of 40 should be the same as before the Act. Allowing 20% for betterment, the basic income of specialists at 40 would have been £2,200, instead of as now £2,750. For specialists there was something of a ladder—payment increased with age and ability—but payments to general practitioners were not similarly progressive. For the general practitioner—the "forgotten man" of the Health Service—he saw no solution short of health centres, and owing to present chronic capital starvation it would be long before these were established in any number. He hoped also that the National Health Service, in place of the present tripartite set-up, would be unified on the basis of local government with larger areas, though not hospital regions, which were too large for practical management; but this was 10 years ahead.

Planning and Co-ordination

The final session was on planning and co-ordination, opened by Dr. W. G. PATTERSON, senior administrative medical officer, Newcastle-upon-Tyne Regional Hospital Board. Dr. Patterson expressed the view that since July, 1948, the hospital and specialist service had advanced more than it would have done under the old regime. Whether regional hospital boards were to have a long life or not, they had got rid of the major and common administrative problem of the health authority which had not made reasonable use of its opportunities from 1929 onwards, and again after the war, to develop a good municipal service in association with the voluntary hospitals of its area. Another awkward problem which had disappeared was that of securing efficient planning and co-ordination between voluntary and municipal hospital systems. When the Act came in he had thought it might take 10 years to secure this happy amalgamation. "I feel now that well before 1958 few will recall often that before 1948 there were two separate hospital systems."

Dr. Patterson went on to speak about general practitioners on regional hospital boards.

"I find myself not infrequently in the peculiar position of having to remind my most enlightened regional hospital board of a possible general-practitioner point of view with regard to some proposal before the board. The doctor representation on the regional hospital board is predominantly a specialist representation and predominantly a teaching hospital specialist representation."

He was convinced that the small representation of general practitioners on the boards was an important factor in explaining some failure in co-operation.

Dr. Patterson also spoke of the need for liaison committees in a hospital region—several liaison committees composed of members of the local health and sanitary authorities, executive councils, and hospital management committees, each liaison committee probably covering a population of about 300,000. Such liaison committees should include both medical and non-medical members from the respective authorities. He left it an open question whether they should also include members from local medical committees.

On the employment of general practitioners in hospitals, Dr. Patterson was convinced that the best domiciliary general practice was found where practitioners also attended patients in a good cottage hospital. "Some of the best hospitals are cottage hospitals where most general practitioners in the neighbourhood are on the staff and which are visited regularly by consultants who undertake the major specialist work."

Medical Administration in Hospitals

Sir FREDERICK ALBAN, chairman of the Welsh Regional Hospital Board, said that the teaching hospital group in Cardiff provided a high proportion of the total hospital accommodation, and practically all the accommodation for the acute sick. There was need for close liaison between the teaching hospital management committee and the regional board, and in Wales this had been achieved. He agreed on the paramount importance of medical administration. Although the headquarters staff of the hospital management committee was a replica of the board, there was one important omission—namely, the complete absence of official medical advice and guidance at hospital medical committee staff level. It was true that individual members of the hospital management committee might give useful counsel, but that was not the same thing as advice from a constant source set up for the purpose. There was unquestionably a wide field of higher administration in the hospital service which could be covered only by a medical man of high calibre, with proper status and pay.

Dr. S. L. WRIGHT, M.O.H., Croydon, said that executive councils as a whole were fairly well ahead on co-ordination. General practitioners admittedly were in a difficult situation. They said that they were underpaid, overworked, and lowered in status.

"We cannot help their underpayment by co-ordination; as regards overwork we can help a little on the local authority side with health visitors and so forth, and the integration of general practitioners with the hospital service would raise their status. But I suppose the long-term issue is health centres. As far as I can gather at the moment general practitioners agree with health centres in theory and practice, with the reservation that the health centres must be in somebody else's area of practice and not in their own. I do not blame them for that; I think they are very wise not to be pioneers, and the hint which has fallen from a previous speaker that the health centre is a method by which doctors can be turned into Civil Servants has let the cat out of the bag"

Dr. Wright was a little sceptical of a plethora of committees. There were committees which sat from four to

six, and whose principal business was a talk over a cup of tea, and there were other committees which might be called procreative, and spawned off into innumerable sub-committees. It should be axiomatic in every committee-room that "officers co-ordinate so that members can legislate." If that was done a great deal of time would be saved and frustration avoided.

No resolutions were put to the Conference, but the delegates evidently appreciated the importance of this the first conference to bring together men and women running the various branches of the Health Service.

Reports of Societies

TREATMENT OF DEPRESSION

On March 23 the Section of Psychiatry of the Royal Society of Medicine discussed "The Treatment of Depression." Dr. E. O. LEWIS, president of the Section, was in the chair.

Dr. W. MAYER-GROSS (Dumfries) opened the discussion with an expression of regret that it should be necessary to define depression before going on to consider its treatment. Endogenous depression should be differentiated from those depressions which were reactive to difficult life situations, and he felt that the difficulties involved in differentiating the two in individual cases afforded no excuse for discarding the two terms in favour of what he called "the theory of a continuous scale of intermediaries." He proposed to consider the treatment of the endogenous group, leaving the reactive illnesses to a subsequent speaker.

Risk of Suicide

Dr. Mayer-Gross felt that precautions against suicide were still of paramount importance despite the radical change in outlook produced by E.C.T., and he reminded his audience how mistaken it was to believe that the patient who spoke of suicide would never in fact take his life. He felt that "even a slight suspicion of suicidal inclination" should be followed by removal of the patient to a place permitting of continuous observation, though he realized the difficulties sometimes involved in convincing the patient and his relatives of the necessity for this course. Where this risk was absent, pharmacological methods, such as the prescription of amphetamine sulphate, had a real place, quite apart from encouragement and reassurance. He drew attention to the deterioration which often occurred in the physical state of depressive patients during the period of tedious and often unnecessary investigation to which they were sometimes submitted by physicians who were having trouble with the diagnosis. It appeared that less emaciation was now necessary before the patient was referred for psychiatric treatment than was the case a few years ago.

With some vigour Dr. Mayer-Gross denounced that excrescence upon the face of psychiatry which had been called "intensive E.C.T.," and he reported that he had seen some lasting memory defects in patients subjected to it. In dealing with E.C.T. in the ordinary sense, he stressed the importance of adapting frequency and number of treatments to the clinical pattern, and pointed out that with very few exceptions the customary complaints of memory defect soon disappeared. With elderly patients, the possibility of memory impairment had to be balanced against the misery and dangers of depressive illness.

Recovery Rate with Electroplexy

Recurrent depression of the usual manic-depressive type did not respond as well to E.C.T. as the involutional states, though this treatment still afforded a chance of recovery immeasurably superior to anything produced hitherto. Success was most likely to be attained if the illness had passed its peak and was waning in intensity, and reference to the patient's habit during previous illnesses would often afford a clue to the time when this peak might be expected. On the other hand the speaker had no doubt about the importance of using E.C.T. in the early stages of an attack to prevent its full development.

A sad though attentive audience showed distinct signs of animation at the unusual sight of Dr. Mayer-Gross divesting himself of his robe of benevolence when he proceeded to deal severely with Karagulla's recent claims[1] that neither the recovery rate nor the duration of stay in hospital differed materially whether treatment was conservative only or by E.C.T. With these conclusions, so patently absurd to anyone engaged in the practice of psychiatry, Dr. Mayer-Gross felt he ought to deal; and deal with them he did. With a tribute to the statistical inspiration of Dr. Eliot Slater, he proceeded to lay bare the fallacies in Karagulla's arguments. Resuming his mantle, and with a last expression of deep regret in which there was much sorrow and no anger, the speaker went on to relate his own experiences at the Crichton Royal, and it was clear enough that the high recovery rate with electroplexy corresponded closely with what most of his audience had found to be true.

Origins of Depression

Dr. W. CLIFFORD M. SCOTT (London), speaking as a psycho-analyst, then followed with an account of his results in the treatment of endogenous depression. He began by lamenting the scant attention given by psychologists to the phenomena of normal depression and mourning, and the incorrigible interest shown by analysts in schizophrenia, both of which factors had impeded progress in understanding the psychopathology of depression. He believed that depression emerged when the infant was still dominated by feelings of love and hate predominantly connected with oral satisfactions; and therefore during the time when people were sources of oral satisfaction. There was some evidence for two possibilities, of which the first was that the constitutional aspect of manic-depressive disorder was to be found in a greater pleasure being connected with oral activities; and the second that it lay in a greater capacity for focusing rage in the oral zone.

In a series of 67 depressives of the endogenous type, Dr. Scott had advised psycho-analysis in 48, and 31 in fact accepted it. In five cases subjected to psycho-analysis, who had received E.C.T. previously, he had not found that the analysis had been helped by the physical treatment. On the other hand two patients gave up analysis in order to have E.C.T. In a series of 18 patients analysed by himself he had obtained good results in 14, and poor results in four.

Differentiation of Endogenous and Reactive Depression

Dr. GERALD GARMANY (London) agreed with the first speaker that some definition appeared to be necessary, and in particular that it should be clear that being depressed did not always involve having a depression in the psychiatric meaning of that word. Confusion between adjective and substantive appeared to be a source of great intellectual difficulty with some pyschiatrists, who became perplexed and troubled if a schizophrenic in their care was unwise enough to betray the slightest sign of affect. Many "atypical" psychoses were in fact in perfect harmony with nosological standards established and accepted for half a century. He felt the difficulty in differentiating reactive and endogenous illnesses in single cases was a good reason for fostering "the theory of a continuous scale of intermediaries" while making a quantitative estimate of the proportion contributed by each. He felt this was but a slight shift of emphasis from what had been said by Dr. Mayer-Gross, and that in practice both would defend the right of black and white to live in harmony with various shades of grey.

In a study of 58 consecutive cases of depression treated as out-patients at the Westminster Hospital an attempt had been made to distinguish the two types. During this period no patient had been sent to a mental hospital

because of depression, so that the series was representative, except that involutional depressions had been excluded. Endogenous depression had been assessed by the usual standards—namely, that it arrived without precipitants, its content was depressive rather than topical, and there might be a depressive personality and a positive family history. There was less response to encouragement, early waking, and diurnal variation of mood. Of these 58 patients 26 had been cured in the strict sense of the word, 23 much improved, and nine were failures. The series showed very clearly the disadvantages of a basically anxious personality when having a depression, and how false it was to believe that reactive depressions were always unsuitable for E.C.T.

Treatment as Out-patients

At the Westminster Hospital it had been found that making E.C.T. available on any day required and at short notice had greatly reduced the number of patients sent to hospital for depression alone. With the co-operation of the anaesthetists, C10 was available for those requiring it; and much use had been made of Fabing's technique in the treatment of depression associated with much tension.[2] Marked loss of weight was generally a contraindication to out-patient treatment, for these patients usually required modified insulin therapy as well.

The Discussion

In the subsequent discussion Dr. W. SARGANT stressed the importance of early waking, diurnal variation of mood, and absence of anxiety, linking these things with a good prognosis. Dr. A. S. PATERSON (London) thought the type of electricity was very important in not stopping the menses, though Dr. Mayer-Gross was unable to agree, having found the products of the Scottish mains to be without effect upon regular menstruation. Dr. ERIC STRAUSS (London) regretted that time did not permit him to say how much he disagreed with everybody. He had not found early wakening or diurnal variation very helpful, and he believed that the incidence of recovery in depression was even higher than had been reported. He found it difficult to assess the effect of psycho-analysis extending over years, since the natural course of a depression was often about six months. Dr. Scott's unperturbed reply was to the effect that he did not merely cure the illness but tried to eradicate the tendency to it as well. Dr. DESMOND CURRAN (London) set a new pattern for the evening by asking a question and making no statement. He asked how long was it justifiable to wait during an illness before recommending leucotomy, as many cases responded to E.C.T. after initial failure. Dr. Mayer-Gross obviously voiced the general feeling when he said the problem was very worrying and needed further research. Dr. M. ROTH (Chichester) talked a little about confusional states and G.P.I., and felt that the effect of E.C.T. was to reverse recently acquired patterns and push back the patient into the state of integration which had previously been held with most stability. After brief replies by the openers, which have been outlined above, a large and happy meeting broke up into forlorn little units and went home.

1 Karagulla, S., *J. ment. Sci.*, 1950, **96**, 1060.
2 Fabing, H. D., *Amer. J. Psychiat.*, 1948, **105**, 435.

This year the British Standards movement attains its Golden Jubilee, and as a part of the celebrations an exhibition, supported by practically the whole range of British industry, will be held at the Science Museum, South Kensington, during the two weeks beginning June 18. Britain was the first country to put industrial standardization on an organized basis nationally through the British Standards Institution. The benefits derived from standards, standardization, and simplification will be graphically presented, and each industry will show how standards have simplified production, reduced costs, and maintained quality, and how in turn they have benefited the user.

Correspondence

Jubilee of Representative Body

SIR,—In July, 1953, the Association will, I feel sure, desire to celebrate the 50th anniversary of the first Representative Meeting, which in 1903 met at Swansea. As the sole survivor of the Constitution Committee whose report revolutionized the constitution of the Association and created the Representative Body I should like to place on record my impressions of that Committee and its work as well as of the Swansea meeting. It would be a great help if any members who were (1) at the Manchester Conference in May, 1900, which set the ball rolling, (2) at the Cheltenham Annual Meeting in 1901, which passed the report of the Constitution Committee, or (3) were members of the Representative Body at Swansea, would favour me with their reminiscences of that eventful period in the history of our Association. They would greatly increase the value of anything I may write and would of course be acknowledged in my article. My address is 17, Trevor Place, London, S.W.7.—I am, etc.,

London, S.W.7. ALFRED COX.

Fungus Infections of the Skin

SIR,—I was interested to read Dr. F. Ray Bettley's instructive article (January 6, p. 28) on fungus infections, but I feel I must draw attention to the dangers of prolonged application of keratolytics to the toes in treatment. This is something which can be done, and is done not infrequently, in temperate climates with relative (but far from complete) impunity. In the Tropics, however, where, curiously, toe fungus infections tend to die out with the development of body infections, I have seen so many drastic effects following keratolytic therapy—from mild eczematization to extensive vesiculo-bullous dermatitis with exfoliation of hands and feet—that I now urge most strongly that such fungicides (including Whitfield's ointment) should be used on the toes particularly, but also on the feet generally, for only very limited periods if at all.

There is another point of importance. The vesicular eruptions of the sole, which may be primarily of fungus origin, may also be a sensitivity reaction (an "ide") from an interdigital tinea, in which case no fungus can be demonstrated in the vesicles on microscopical examination or culture. This latter state of affairs is common in the Tropics, and not uncommon in temperate climates. Fungicides are contraindicated in such cases. Treatment should be as for an eczematous condition, except that the toes should be treated with a non-keratolytic fungicide.

Interdigital foot tinea, which fluctuates in winter and summer, is very common and very difficult to demonstrate, particularly when the condition is quiescent. Dr. Jacqueline Walker's report of a 3.8% incidence I consider to be far too low. Legge, Bonar, and Templeton[1] found a 78% incidence in 3,100 California University students, admittedly not quite a comparable group, but also showed that cultural success could be increased from 32% to 66% by making more determined efforts.

Finally I contend that so-called "dhobie itch" is a complete misnomer, and that laundry facilities are in no way responsible for the development of crutch tinea in the vast majority of cases. Body tinea develops in the European in the Tropics in almost every case inside the first four months after his arrival (60 out of 64 consecutive cases in my series), and this I believe is largely due to a variation of *T. interdigitale*, brought out from the temperate zones between the toes, into *T. mentagrophytes*. In support of this it may be noted that the introduction of steam laundering for troops in Hong Kong has not succeeded in reducing the incidence of body tinea at all.—I am, etc.,

Singapore. KEMBLE GREENWOOD.

REFERENCE

1 *Arch. Derm. Syph., Chicago*, 1933, **27**, 12

Syringe Needles and Mass Inoculation

SIR,—The article by Sir Alexander Fleming and Dr. A. C. Ogilvie (March 17, p. 543) is of great interest and importance to all whose work includes the giving of hypodermic injections in whatever number. Their recommendation that needle sterilization should be effected by a 130° C. oil bath may be easy to arrange in hospitals and large clinics but will not be easy to arrange in general practice. There would be difficulty in finding a suitable sterilizer and in keeping the temperature steady over long periods. Would not the addition of 1 or 2% sodium carbonate to the water of an ordinary electric or gas sterilizer kept on the boil accomplish the same results? The alkalinity increases the bactericidal effect of boiling water sufficiently, I imagine, to reduce the ten-second immersion period recommended for ordinary water; and also it prevents rusting and consequent blunting of steel needles and instruments. An alkaline solution might destroy certain injections, but simple needle-immersion would probably not bring sufficient alkali into contact with the injection fluid to do this.

For some years I have kept such a solution boiling in my surgery sterilizer throughout the session and always dip my syringe needle in it before giving an injection. Also it takes needles, scissors, scalpels, etc., without causing premature blunting.

Is the fear of blunting sharp steel instruments by boiling founded on fact? I think that it may be one of those fancies handed down from one person to another until it becomes an accepted fact. When visiting the Birmingham Accident Hospital I noted that it was routine practice to boil scissors, scalpels, needles, and everything else used in their excision and suture technique, which is carried out many thousands of times a month. No increased tendency to blunting was noted even after many immersions. The simplicity of this form of sterilization has much to recommend it when there is a big turn-over of dirty industrial cases and not always sufficient time to use cold chemical solutions for sterilizing steel instruments.

It would be interesting to know whether Sir Alexander Fleming and Dr. Ogilvie would approve of this form of needle sterilization as a satisfactory alternative to the hot-oil bath and also whether there is any reliable evidence that steel sharpness is really affected by boiling water to which 1 or 2% sodium carbonate has been added.—I am, etc.,

Sheffield. E. C. ATKINSON.

Contamination of Hospital Fluids

SIR,—During a search for the reservoirs and routes of added infection in wounds, we have recently sampled a number of bottles containing fluids used in hospital dressing stations and operating theatres. A large proportion of the swabs taken from bottles of soap solution and calamine lotion were shown to contain *Ps. pyocyanea*, and some bottles of 1% cetrimide solution and 10% "dettol" were also found to contain this organism. The contaminated bottles had corks, and some of them were large stock bottles which were frequently opened and infrequently refilled.

This source of wound infection can easily be stopped by dispensing all hospital fluids in screw-cap bottles sterilized before or, if possible, after filling with the fluid. Small bottles are recommended, so that they can be replaced at frequent intervals; this would reduce the chances of contamination—for example, from fingers—and allow less time for multiplication to occur. Our evidence suggests that the cork is a nidus in which the organism may be preserved and multiply even in the presence of such disinfectants as cetrimide and dettol.

Swabs taken from hospital fluids dispensed in sterile screw-cap bottles have so far yielded no growth of *Ps. pyocyanea*, and there is evidence that replacement of the old by the new method of dispensing fluids has been followed in one hospital by a reduced incidence of *Ps. pyocyanea* in wounds. These findings are reported in detail elsewhere.[1]

The risk of contaminating wounds from fluids used in their treatment has long been recognized. The reason for re-emphasizing the risk is that we found it to be a high one that was amenable to a simple remedy. There is a strong case both for the more frequent bacteriological sampling of hospital fluids in routine use and for the introduction of suitable sterile screw-cap bottles in place of corked bottles. The use of sterile fluids should in our opinion be one of the essential components of the modern no-touch aseptic dressing technique.[2]—We are, etc.,

W. RECHT.
E. J. L. LOWBURY.
E. TOPLEY.

Birmingham.

REFERENCES

1 Lowbury, E. J. L., *Brit. J. industr. Med.*, 1951, **8**, 22.
2 Medical Research Council War Memorandum No. 6, 1941.

Analgesia for Urethral Instrumentation

SIR,—During the last three years we have put to extensive use the following preparation: 0.5% amethocaine hydrochloride and 0.5% phenol in distilled water. The solution is sterilized by boiling and can then be kept in large bottles indefinitely. The phenol prevents the growth of bacteria and moulds, and even after many months of use and constant opening and closing of the bottle the solution remains perfectly clear and sterile.

Before instrumentation 30 ml. of the solution is instilled into the urethra with a suitable syringe, and is held there under pressure for five minutes or longer. After this the patient can be cystoscoped or catheterized with complete comfort, although the prostatic urethra remains somewhat sensitive. Ureteric catheterization can be done with the help of this local analgesic agent.

So far, in thousands of cases, we have not had a single untoward reaction, and it would seem that the mild antiseptic properties of this mixture lend a certain measure of safety to the passage of instruments via the urethra into the bladder. The solution is simply prepared, and its safety and efficacy have made it a real boon in our urological clinics.

The injection therapy of hydroceles is now a well-established procedure. Quinine urethane causes little constitutional reaction, but its effect is uncertain and often disappointing. "Ethamolin" produces consistent results, but its injection into the hydrocele sac is often followed by syncope some minutes later. These alarming faints can be almost completely abolished if the tunica is anaesthetized by introducing 20 ml. of 0.5% amethocaine hydrochloride and 0.5% phenol into the sac after it has been emptied of hydrocele fluid. Ten minutes later the analgesic solution is drawn off and replaced by anything between 1 and 5 ml. of ethamolin according to the size of the hydrocele. We take the additional precaution of giving the patient 50 to 100 mg. of pethidine intravenously and keeping him recumbent for the next 30 minutes. He attends weekly for aspiration of the reactionary hydrocele fluid until it fails to re-form, perhaps in three or four weeks. Scrupulous asepsis is more than essential in every step of the whole procedure. Complete cure has followed this treatment in all our cases and obviated the need for surgery. The patient is warned that the testicle will remain larger than its neighbour for at least a year.

We have not treated young boys or adolescents in this way for fear of impairing spermatogenesis, but would be glad to have the opinion of your more experienced readers.—I am, etc.,

Chelmsford, Essex. M. D. SHEPPARD.

Retrolental Fibroplasia

SIR,—With reference to the paper by Mr. Joseph Minton and Dr. Pauline Cole (March 3, p. 450) and your annotation (p. 466) on retrolental fibroplasia certain questions seem to arise. What is the reason that retrolental fibroplasia was first described only in 1942? Why is the disease so much more common in Boston[1] than in Baltimore[2] or Cincinatti[3]? Why is the incidence so much less frequent in Great Britain[4] and the disease nearly unknown in Switzerland and other

Continental countries[5] ? Are Owens and Owens[6] right when they discuss the endeavour of paediatricians to reduce the mortality of premature infants and ask how far the modern special diets, large doses of vitamins, transfusions, hormonal treatment, and other well-intended therapeutic measures could be responsible for some metabolic interference which directly or indirectly might lead to the development of retrolental fibroplasia ? In support of this concept, in a pilot experiment they demonstrated that of 23 premature infants with a birth weight of 1,360 g. (3 lb.) or less receiving alpha-tocopherol acetate only one (4.4%) developed retrolental fibroplasia, while of 78 infants of the same birth weight without vitamin E supplement 17 (21.8%) developed the disease.

It is, of course, not intended to imply that vitamin-E deficiency has any direct effect in the production of this disease. It is, however, of interest to record that nutritional science may be of some help in the elucidation of the aetiology of some puzzling conditions, including retrolental fibroplasia.—I am, etc.,

London, W.1. Z. A. LEITNER.

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3 Gilger, A. P., ibid., 1949, **32**, 917.
4 Minton, J., and Cole, P., *British Medical Journal*, 1951, **1**, 450.
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6 *Amer. J. Ophthal.*, 1949, **32**, 1631.

Low Spinal Block in Eclampsia

SIR,—Drs. V. H. Cooper and P. V. Lang described on February 17 (p. 338) a primigravida of 26 who developed eclampsia during labour and was apparently saved by a low spinal block. Somehow, according to them, it broke the "vicious circle of rising blood pressure."

The case interested me greatly, for in 1928 I related a similar experience, though my patient was not in labour; and, subsequently, several like cases ("Eclampsia and its Treatment: An Experience with Spinal Anaesthesia in One Case," *Proc. R. Soc. Med.*, Sec. Obstet. and Gynaec., 1928, **21**, 70; "A Case of Eclampsia Treated with Spinal Anaesthesia," *British Medical Journal*, 1930, **1**, 15; "A Case of Eclampsia Treated with Spinal Anaesthesia," *Lancet*, 1930, **2**, 399; "Two Cases of Postpartum Eclampsia," *J. Obstet. Gynaec. Brit. Emp.*, 1933, **40**, 843; "A Case of Eclampsia," ibid., 1934, **41**, 978; "Anuria Treated with Spinal Anaesthesia," *Lancet*, 1935, **2**, 554).

I believe I was the first in this or any country to induce spinal anaesthesia in these cases as a purely therapeutic measure—not for its anaesthetic effect, not as a prelude to any operation. I had come to this by inductive reasoning. Long before, I had reached the opinion that the toxaemias of pregnancy result from visceral circulatory difficulties caused by undue activity of the abdominal wall muscles. I argued, if one can reduce the tonicity of the abdominal wall musculature, the compression of the kidneys (and of the liver) will be relieved, blood will flow through them as it should, and the pathological state of the woman will disappear. In spite of this idea, which gradually arose and impressed itself on me, it was not till 1926 or so that somehow or other I tumbled to the idea that the induction of spinal anaesthesia appeared the method of choice to apply in cases of eclampsia, though previously I had been using spinal anaesthesia in my gynaecological and obstetric operations (caesareans) and obtaining an amazing relaxation of the abdominal wall muscles.

I have one criticism to make in respect of the case reported. Drs. Cooper and Lang refer to the albumin in the urine passed by their patient, but say nothing about the urine volume. But the presence of albumin in the urine of pregnant women who were quite well at the beginning of their pregnancy is only of secondary importance: the thing that matters is the amount passed. Women with urine containing no albumin may become eclamptic: in such cases it is only after the first eclamptic fit, by which the kidneys are greatly compressed, that the urine comes to contain albumin. I used to say to my primigravidous patients: "As long as you are passing plenty of water you are safe"; and to thunder to myself—for lack of a larger audience—that diuresis and eclampsia are incompatibles.—I am, etc.,

Rugby. R. H. PARAMORE.

Chemotherapy in Cholera

SIR,—I have read with great interest the article (March 10, p. 500) by Dr. S. C. Lahiri and your editorial comment on it. I would like to make a few remarks on it as a general practitioner doing community medical service in an industrial area near Calcutta for the last seven years until I left for the U.K. in September, 1950.

The hygienic condition of the industrial area is very bad and epidemics of cholera are very frequent. As hospital accommodation is very limited, we have to undertake the treatment of the cases with as much segregation as possible. As may be expected, the cases are all diagnosed clinically and no laboratory help is available. The cases usually call for our attention in an early stage in comparison with the hospital patients whose conditions are usually very bad.

The bugbear with the treatment of cholera in the early stage is to control the vomiting, for which we use our time-honoured drug, calomel powder with chloretone. If the vomiting be controlled, we can give fluid by mouth in the form of *dub* (green coconut) water. Depending on the degree of dehydration, which we assess clinically, saline solution (isotonic, hypertonic, and alkaline) is administered intravenously, and other complications are treated. We also used sulphaguanidine tablets, with no appreciable good results.

In 1950, from April to July, I got 37 cases, in which I adopted the following line of treatment. Empirically I used an antihistamine drug ("antistin") intramuscularly in all the early cases for the control of vomiting—usually the vomiting stops within 15 minutes. Then formosulphathiazole tablets were administered in doses of 2 g. every three hours along with *dub* water. Out of 37 cases, I had to use saline only in three cases, and only one case died.

While I highly appreciate the scientific way Dr. Lahiri carried out his work, and while I admit my limitation as a general practitioner, I still hold the view that there is a field for chemotherapy, especially with formosulphathiazole, in the treatment of cholera cases in the early stage.—I am, etc.,

Portobello, Midlothian. B. BHAR.

Treatment of Naevi

SIR,—The recent correspondence on angiomatous birthmarks has shown the gradually increasing recognition of the importance of Lister's observation that spontaneous disappearance is the rule (Dr. C. M. Ross, February 17, p. 356; Dr. R. E. Bowers, January 20, p. 121; Mr. D. Browne, March 3, p. 474; Dr. N. S. Finzi, March 10, p. 530). In a series that I followed up recently for three to five years well over 90% were found to disappear spontaneously; the result was communicated to the Sixth International Congress of Radiology in London, July, 1950, and I hope to publish the details shortly. Dr. Finzi and Dr. Ross are right in stressing mucosal lesions, notably on the lip, as possible exceptions to the general rule of disappearance. In my own series there were 23 lip cases, with satisfactory results in 18 (78%), compared with an overall figure for all lesions of about 95%. In the cases deliberately left untreated in the series there were only two lip lesions, both of which disappeared of themselves. Spontaneous regression is therefore certainly possible but is, I think, slower and far less certain than elsewhere. One point is perhaps worth noting: in four out of the five lip lesions that responded only imperfectly to treatment the clinical impression was of fibrous rather than angiomatous residues. Fibrous residues, in this series, were far commoner here than in other sites.—I am, etc.,

Sheffield. J. WALTER.

Exchange Transfusion Methods

SIR,—Dr. M. S. Fraser (March 3, p. 75) asks whether anyone in this country has used the radial artery procedure for exsanguination, and he comments upon the danger of overloading the circulation of an anaemic infant, when the volume of blood introduced is greater than that extracted.

In February, 1948, I was asked to perform an exchange transfusion on a 6-lb. (2.7-kg.) baby who was 48 hours old. A "topping up" transfusion had been given on the first day of life, and at the time the exchange was attempted he was not anaemic, but was profoundly jaundiced and showed early signs of kernicterus. I did not heparinize the infant, but gave blood into the saphenous vein, and made an open cut into the radial artery for exsanguination. By this method I found it impossible to measure accurately the amount of blood withdrawn, and therefore we introduced a small metal cannula into the artery. In spite of irrigating the cannula with heparin-saline, the flow of blood was inadequate, and the procedure was abandoned after an exchange transfusion of about 60 ml. had been made. There is probably no justification for performing exchange transfusions upon an infant of 24 hours or more, but if I were again to attempt such an operation I would use the femoral vein.

Two infants with icterus gravis and severe anaemia had transient signs of circulatory overloading following exchange transfusions via the umbilical vein. The babies were not distressed while the exchange was being performed, but the circulation was embarrassed by the "extra" 60–100 ml. of blood given gradually with a syringe. In subsequent cases excess blood has been given immediately after the exchange operation, but as a very slow drip, and there has been no evidence of overloading.—I am, etc.,

Hereford. J. LORD

Anti-Lewis in Transfusion Haemolysis

SIR,—We have read the article by Dr. S. I. de Vries and Miss H. S. Smitskamp (February 10, p. 280) describing the Lewis antibody (anti-Le^a) present in their patient's serum and active at 37° C. We desire to draw attention to the fact that the statement that "this antibody has given rise to a haemolytic transfusion reaction" lacks evidence to support it. Apparently it has not been possible to demonstrate, for example, the fact that the transfused erythrocytes were abnormally rapidly eliminated from the recipient's circulation. Again, it has not been shown by haemoglobin estimation whether the patient derived benefit from the transfusion. Moreover, no account is given of the state of the blood with which the patient was transfused, or its age. If stored blood was transfused it is manifestly important to know how old it was when transfused and also whether it was simply citrated blood or citrated blood preserved with glucose. Does the presence of agglutinins in the recipient's serum and active *in vitro* at 37° C. necessarily mean that the transfusion reaction was due to that agglutinin? It is doubtful, since the authors state there was a cold agglutinin still active at body temperature.

The blood of three different donors was transfused, a total of 1,500 ml., but the authors report only the investigations on the bloods of the first and second donors. What was the blood group of the third donor? Why is no account given of the reactions between the serum of the recipient and the red cells of the third donor? Is it to be assumed, in the absence of supporting evidence, that the blood of the third donor was strictly compatible? We note that no mention is made of tests for incompatibility between the iso-agglutinins of the three donors used and the recipient's red cells. The claim that the haemolytic reaction described was attributable to the anti-Le^a agglutinin is clearly not substantiated by the evidence given.

In cases of this nature in which haemolytic transfusion reactions are attributed to atypical agglutinins in the serum of the recipient one should demonstrate not only changes in the titre of the suspect agglutinin but also that the transfused erythrocytes undergo abnormally rapid elimination from the recipient's circulation. Studies on the *in vivo* survival of the transfused erythrocyte are desirable, because it is essential to demonstrate that the transfused red cells, and not those of the recipient, are the ones which are destroyed.

When haemolysis complicates transfusion it is necessary to establish whether or not the donor blood was effete when transfused and whether it had been properly stored and handled—for example, had not been frozen or overheated. Haemolytic reactions may, for example, complicate transfusion of three or four bottles of compatible but aged blood, albeit not time-expired (see R. Drummond, *Medical Press*, 1949, **222**, 325). It is manifestly important, when deciding whether or not an atypical agglutinin in a recipient's serum is the cause of a haemolytic reaction, that all the various points we have mentioned should receive detailed consideration and should be included in the case report.—We are, etc.,

Regional Transfusion Centre, Manchester Royal Infirmary. F. STRATTON.
Regional Transfusion Centre, Newport Road, Cardiff. R. J. DRUMMOND

Islet-cell Tumour of the Pancreas

SIR,—The very interesting case report of Dr. F. J. Y. Wood (March 3, p. 457) prompts me to suggest that Whipple's diagnostic criteria for the diagnosis of hyperinsulinism need not be completely fulfilled for the establishment of the diagnosis of islet-cell tumour of the pancreas in all cases. This makes the already complicated picture more uncertain, and, as the following case will show, it was previous intimate clinical experience of hypoglycaemia and not blood-sugar curves which gave the clue to diagnosis and cure. It also illustrates that it may be only the family doctor who, by repeated questioning and by being first on the spot at the onset of the coma, may have the chance to see the crucial symptoms and signs.

A girl of 21, training to be a teacher, was well until 1948. She has had no previous illness except whooping-cough, measles, and chicken-pox, and there was no relevant family history. She was an athletic type, 5 ft. 2 in. in height.

In January, 1948, it was noticed that she became easily tired and was yawning a lot, so much that it was jokingly referred to as "sleeping sickness." In November, 1948, she had to be put to bed on account of "general weakness." The doctor and a psychologist who were called in could not account for her state. She soon carried on with her work again, but there was another bout of yawning and tiredness in April, 1949. In June her legs suddenly gave way for about five minutes, and it was noticed that her face had a wooden expression. In August she had an attack of twitching of her hands and face, but was not aware of her condition. All the time her face appeared again wooden, uncanny, somewhat oedematous. In September she got her first appointment as a teacher. In November she noticed weakness in the knees, had transient turns of not being able to speak, and became on one occasion unconscious for a short time. She was examined, but nothing could be found and rest was ordered.

On December 24 she went into a deep coma and was admitted to hospital. She came out of the coma, and relapsed back into it three or four times, for periods of from 48 hours to one week. After three to four weeks she was transferred in a comatose state to another hospital for further investigations. She was then deeply unconscious and in a state of decerebrate rigidity. The possibility of a cerebral tumour was considered and a ventriculography was done, but was completely normal. An E.E.G. did not show anything significant. The blood-sugar examinations were suggestive of hypoglycaemia, being 55 and 50 mg., but glucose-tolerance curves were within normal limits, and it was not considered that she could be a case of spontaneous hypoglycaemia.

She recovered from the coma, but was left with aphonia and complete left hemiplegia, which was considered to be due to cerebral thrombosis. The aphonia, which disappeared under speech therapy, was thought to be hysterical in nature, and during her recovery she produced "psychogenic" symptoms and gave the impression of a schizoid type. A few days after her discharge from hospital at the end of March, 1950, she had an attack at home lasting three-quarters of an hour, during which she was flinging her limbs and body purposelessly about and of which she remembers nothing; it was thought to have looked like an epileptic fit.

I saw her for the first time in August, and from then on frequently. At this time she was subject to slight attacks of weakness and drowsiness at irregular times of the day and was difficult to rouse in the mornings, but on repeated careful examination I could not find anything abnormal physically. Mentally she appeared somewhat retarded, slow in answering, at times with a schizoid smile or an expressionless face. On August 21, however, when called to see her urgently, I found her lying on the floor in a semicomatose state throwing her arms and legs as well as her body about, covered with beads of perspiration, with wide pupils and a rapid pulse.

Some years back, when giving high doses of insulin to schizophrenic patients daily for about a year, I found this was exactly the state that was produced each time one to two hours after the injection. The similarity was so striking that there was no doubt in my mind that the patient was in an advanced state of hypoglycaemia. As she could not swallow, it was not possible to give her a sugar solution by mouth. She was sent to hospital with the diagnosis of hypoglycaemic coma. A laparotomy was performed and an islet-cell tumour of the pancreas removed. She made a quick recovery and has not had the slightest attack since. The hemiplegia has unfortunately not much improved, but she manages to walk about quite briskly with the aid of a stick, and is back at work in her profession.

The case well illustrates the two features pointed out by Dr. Wood and which are known to be characteristic of islet-cell tumour of the pancreas—namely, the tendency to spontaneous recovery from the hypoglycaemia, and the lack of correlation between clinical attacks and the blood-sugar level. Another interesting feature was the fact that slight brownish pigmentations previously noticed on the forehead and back of the hands disappeared after the operation. Deep hypoglycaemia is rarely seen except in mental hospitals and sometimes in diabetics.—I am, etc.,

London Colney, Herts. F. P. DURAS.

Infection after Lumbar Puncture

SIR,—Dr. R. Bryce-Smith and Professor R. R. Macintosh (February 10, p. 275) advance an ingenious theory to explain the occurrence of sixth-nerve palsy after lumbar puncture. As they admit, proof is difficult, and the exact cause must remain speculative. I do feel, however, that they dismiss low-grade infection as a possible cause both of the nerve lesion and of post-puncture headache too easily. The clinical features that they describe correspond to meningeal irritation, and absence of fever cannot entirely rule out an evanescent low-grade infection.

Prolonged seepage of cerebrospinal fluid as a cause of headache has always seemed to me an unsatisfactory explanation. Kremer[1] pointed out that patients with open wounds of the brain and leakage of cerebrospinal fluid do not complain of similar headaches. On the other hand, there is a lot of evidence to show that infection by non-pathogenic organisms is commoner than is ordinarily supposed.[2,3]

In my own practice the incidence of post-puncture headache has varied directly with the efficiency of the aseptic technique employed. The highest incidence was while working in a Japanese internment camp, when a stiff neck and severe headache were not uncommon sequelae of a spinal analgesic Before the war the incidence was 10–15%: gloves were not used, and instruments were boiled and placed in a sterile dish filled with sterile distilled water. Since 1946 full aseptic technique and dry instruments have been used, and careful preparation of the skin of the back has been carried out. In spite of careful inquiry from ward staffs I have not seen a severe instance of post-puncture headache. Although aseptic precautions varied, the technique employed, the size of needle (Howard Jones), and the analgesic agent (1/1,500 light "nupercaine") remained the same throughout the whole period.

From these observations one is driven to the conclusion that the severer type of post-puncture headache must be caused on many occasions by a slip-up of aseptic technique. The occurrence of such a complication should be the signal for a thorough overhaul of aseptic technique and the preparation of the patient. It would be a pity to allow the theory of leakage of cerebrospinal fluid, about which little of a preventive nature can be done, to drive into the background a very real and proved danger (infection by non-pathogenic organisms) and probable cause of headache which is to a large extent preventable.—I am, etc.,

Rochdale, Lancs. D. A. B. HOPKIN.

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Oral Penicillin and Gastric Acidity

SIR,—The communication from Dr. S. A. Doxiadis and his colleagues (February 24, p. 415) involves the important question of whether continuous blood penicillin levels are necessary for effective therapy. The work of Ungar,[1] demonstrating the persistence of penicillin in exudate fluids long after its disappearance from the blood, would seem to cast serious doubt on this assumption. This is a view which has recently received support from Sir Alexander Fleming.[2]

Doxiadis and his colleagues suggest that if allowance is made for lowered gastric acidity in illness oral penicillin dosage may become inadequate as the patient recovers and his gastric acidity increases. It might be equally well argued that, as the patient recovers, the amount of penicillin required diminishes. In practice this problem does not arise, since large doses must always be administered to allow for individual variations in absorption.

The question of economy should not be allowed to bar scientific investigation; in any case trials with "aureomycin" and chloramphenicol must cost considerably more than any similar procedure with oral penicillin. Another factor is the saving of doctors' time. Surely this is worth some increase in the cost of treatment?

I agree with Doxiadis and his colleagues that I would not rely upon oral absorption of penicillin in preference to parenteral administration in a serious illness such as, say, pneumonia. However, there is a wide field of less serious conditions where oral penicillin therapy can be of immense value, both curatively and in the prevention of complications. I would also agree that three-hourly dosage would be most tedious for any patient. In practice I have found six- to eight-hourly dosage equally effective.[3] Certainly my juvenile patients prefer it to even the subcutaneous injection of crystalline penicillin; and this dosage scheme also has the advantage of an uninterrupted night's rest.

I would conclude by reaffirming my plea for further trials of oral penicillin in ill persons, assessment being made on clinical results. Such trials could involve both the comparison between different dosage schedules and comparison with parenteral administration. I feel that the results of such investigations would prove of more value than a knowledge of the doses required to maintain bacteriostatic levels in the blood.—I am, etc.,

Twickenham. DAVID WHEATLEY.

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Sensitivity to Procaine Penicillin

SIR,—I have used procaine penicillin extensively since 1948, and never had reported a case of allergic reaction. It was therefore with great interest that I read yesterday Dr. T. V. Humphrey's letter of February 10 (p. 299), and by rather a strange coincidence to-day a patient of mine reported an allergic reaction.

A week ago he had an injection of procaine penicillin (1 ml.) at midday, and the same evening developed swelling of hands and feet and generalized pains which have kept him from work for the past week. Unfortunately I did not see him during a severe stage of his reaction, but when seen by me to-day there was still some swelling of fingers and feet.—I am, etc.,

Port Maria, Jamaica. H. M. WILKES.

Congenital Abnormalities

SIR,—I wish to correct the erroneous impression that may be created by Mr. G. C. Gordon's statement, "This stunting of growth is an invariable feature of experiments with insulin and other noxious materials. . . ." in his letter (February 3, p. 247). Mr. Gordon will be interested to know that localized deformities or "distortions," as he would prefer to call them, can be induced in chickens with small doses of insulin (0.05 to 1 unit) without any stunting of the general growth. I have made similar observations in the case of deformities of bone induced in chicks with "synthalin," certain sulphonamide compounds, and thallium salts, and also in respect of "myodystrophy" induced in chick embryos with 3-acetyl pyridine injected into the yolk in the same way as insulin.

It seems to me to be fallacious to compare the increase in size of a baby associated with maternal diabetes mellitus with the retardation of general growth induced by *higher* doses of insulin in chickens because, unlike the human foetus, the chick embryo is not at all under maternal endocrine influences during its development. Again, insulin which is injected into the yolk during the first week after the beginning of incubation induces the various abnormalities at a time when the embryonic liver in the chick has not begun to store glycogen in appreciable quantities and the various endocrinal glands are not fully differentiated, as mentioned in my article (*Journal*, August 12, 1950, p. 384).—I am, etc.,

Cincinnati, Ohio. P. K. DURAISWAMI.

POINTS FROM LETTERS

Gastro-enterology in Paris

Dr. W. A. BOURNE (Hove, Sussex) writes: It is not easy to see much foreign work now, but if anyone would like a general view of French gastro-enterology I can recommend a five-day course, to be given at the Hôpital Tenon, 4, Rue de la Chine, Paris 20e, from May 21 to 25. The lectures are in French, but are illustrated by many good *x*-ray films. Dr. Viguie, Laboratoire Marcel-Brule, at the hospital would send details.

Vegetarianism

Mr. H. H. JONES (secretary of the Vegetarian Society, Wilmslow, Manchester) writes: "The confusion [about the definition of "vegetarianism"] which Sir Adolphe Abrahams encounters is due to accepting definitions used by those who were unfamiliar with its origin. The author of *One Hundred Years of the Vegetarian Society* states that the words "vegetarian" and "vegetarianism" were devised about 1842 to replace the inadequate and misleading "vegetable diet." The founders of the Vegetarian Society (1847) were the first users of these words, and from the beginning vegetarianism has been officially designated as "the practice of living on the products of the vegetable kingdom, with or without the addition of eggs and milk and its products." In the booklet already mentioned the following comment is made: "The meaning of the word does not depend on what some people *think* it means, but upon the meaning attached to it originally and established by use. Dr. J. E. B. Mayor, professor of Latin at Cambridge University, showed that the word 'vegetarian' is correctly formed from the Latin word 'vegetus,' which means 'whole, sound, fresh, lively.' It is not a shortened version of 'vegetable-arian' as some have supposed." The *New Oxford Dictionary* definition comes the nearest to the correct interpretation; Stedman's so-called "strict" vegetarian is definitely incorrect and is the opinion of a dietetic cult which avoids anything grown beneath the soil, such as tubers. Dorland's definition is that of the present-day "vegan"—the person who cuts out all foods of animal origin.

Samples

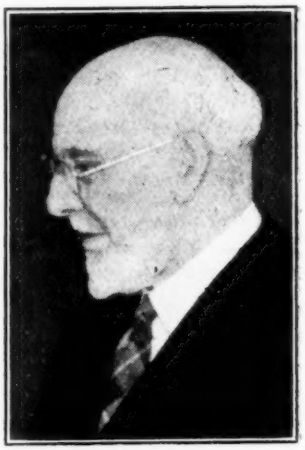
Dr. D. HANBURY (Midhurst, Sussex) writes: I hope that I shall not be considered lacking in gratitude by the donors if I write to you to record my increasing concern at the enormous numbers of samples of proprietary drugs I receive. The ingenuity of the dispenser, the cunning of the manufacturer of fancy packings, and the erudition of those obscure pamphleteers who write the accompanying advertisements amaze me no less than the exotic names of those mentioned in the bibliographies at the end. . . .

Obituary

J. A. NIXON, C.M.G., M.D., F.R.C.P.

Dr. J. A. Nixon, Emeritus Professor of Medicine in the University of Bristol, died on March 17 in the Bristol Royal Infirmary after a short illness. He was 76 years of age.

John Alexander Nixon was born in Edinburgh in 1874. He was educated at Hurstpierpoint, Gonville and Caius College, Cambridge, and St. Bartholomew's Hospital. He showed early promise of his distinguished future, for he was a Tancred student at Cambridge and president of the Abernethian Society and editor of the hospital journal at Bart's. He graduated M.B., B.Ch. in 1900, became an M.R.C.P. in 1903, and was elected F.R.C.P. in 1911. Later he became a councillor and examiner to the College. He proceeded to the degree of M.D. in 1915.



After holding house appointments in London—at St. Bartholomew's and the Metropolitan Hospital—he came to Bristol in 1902 as a resident at the Royal Infirmary and served that hospital for the rest of his life. Nixon was first appointed to the honorary staff in 1906 as physician to the department of diseases of the skin, but combined dermatology with general medicine. He was appointed assistant physician in 1907 and became a full physician in 1909. At various times he also served as physician to Southmead Hospital, Cossham Memorial Hospital, Stoke Park Colony, and Bristol Mental Hospital. On the foundation of Bristol University in 1909 he was appointed clinical lecturer in diseases of the skin and in 1924 became professor of medicine, from which post he retired in 1935. He was elected professor emeritus in the following year. He retained to the end his great interest in medical education, and was external examiner in medicine to the National University of Ireland. His teaching was essentially clear and marked by precision and the closest attention to detail. During the last few years he acted as inspector of the final examination in medicine for the General Medical Council. This work he much enjoyed, since it brought him into touch with teachers and examiners all over the country, and he carried it out with the extreme conscientiousness and care which characterized all his work.

Nixon was one of the early members of the Association of Physicians and was president when the association last met in Bristol. For some years an editor of the *Bristol Medico-Chirurgical Journal*, he was also president of the Bristol Medico-Chirurgical Society in 1922–3 and of the Bath, Bristol, and Somerset Branch of the B.M.A. in 1929–30. He was a valuable member of the Association, serving on several important committees, including for a short time the Journal Committee. An enthusiastic Territorial, he served in

the 1914–18 war as a temporary colonel A.M.S. in France and on the Rhine and for this service was made a C.M.G. in 1919. He kept up his work for the Territorial Army, and was chairman of the Central Organization of the Military Education Committees of Universities and University Colleges. During the last war he gave untiring service to the South-western Region as adviser in medicine.

Nixon's interests in medicine were wide and varied. He was a member of the Industrial Health Research Board of the Medical Research Council and was always interested in occupational diseases, particularly occupational dermatitis. One of the first physicians to use insulin in this country, he quickly realized that it made unnecessary the stringent dietetic restrictions then commonly enforced and was a vigorous advocate of a "high carbohydrate diet" for diabetic patients. Keenly aware of the importance of nutrition in health and disease, his interest in this subject culminated in the valuable *Textbook of Nutrition*, written in collaboration with his wife in 1938. He was keenly interested in the history of medicine, particularly as it concerned the sea and the Navy. On this subject he became an acknowledged authority, making a special study of Thomas Dover, the famous Bristol physician and pirate. His FitzPatrick Lecture to the Royal College of Physicians in 1941 was given on "Health and Sickness in the Merchant Navy."

Professor Nixon was throughout his life a devout churchman and much interested in ecclesiastical history. For nearly fifty years he was an active Freemason, and he took a very lively interest in the work of the local branch of the British Red Cross Society.

In 1924 Professor Nixon married Dr. Doreen Walker. To his widow and to his son and daughter, who is a medical student, we extend our deep sympathy.—C. B. P.

G. A. R. KON, D.Sc., F.R.S.

Dr. G. A. R. Kon, professor of chemistry at the Chester Beatty Research Institute of the Royal Cancer Hospital, London, died in Manchester on March 15, aged 59 years. He was one of the leading authorities in the country on medical chemistry.

George Armand Robert Kon was educated privately and at Caius College, Cambridge, where he took the Natural Sciences Tripos. In 1913 he joined the staff of the Imperial College of Science and Technology, South Kensington, where he carried on research work in organic chemistry under the late Sir Jocelyn Thorpe. During the first world war he served in the anti-gas department and was mentioned in dispatches. He obtained a commission in the Royal Engineers in 1918, and went as a member of the British Gas Mission to the United States. After the war he returned to the Imperial College, becoming a lecturer there in 1925 and assistant professor in 1934. In 1942 he was appointed professor of chemistry (in the University of London) at the Chester Beatty Research Institute of the Royal Cancer Hospital, and in the following year he was elected a Fellow of the Royal Society.

Kon's earlier work was on the tautomeric changes of organic compounds, and one of his particular studies was the intricate group of glutaconic acids. Later he began the investigation of the steroid and triterpene groups of natural products, which have become so important in recent years. One of his greatest achievements was the synthesis of "Diels's hydrocarbon," which is essential for any study of the steroids. From 1942 onwards his studies on the chemistry of cancer at the Chester Beatty Research Institute of the Royal Cancer Hospital were mainly concerned with new types of chemical carcinogen, first in the field of aminostilbene derivatives, and secondly the chloroethylamines ("nitrogen mustards"), diepoxides, and other biological alkylating agents, the investigation of which is still extending and developing on a considerable scale. In both cases much new knowledge has been gained of the relationship between chemical constitution and biological action, and the second, it would seem, also promises to throw much light on the more precise mechanism of carcinogenesis and mutagenesis on the molecular level, at least so far as these particular chemical types are concerned. Professor Kon's knowledge, judgment, and assured technique gave great distinction to his work of research.

A colleague writes: No account of Professor Kon's career would be complete without reference to his modesty, humour, and charm, which so endeared him to his colleagues, or to his talents as a linguist, sportsman, and connoisseur. These qualities, and his professional distinction, earned him a special place among scientists wherever he went.

Dr. A. J. W. WOODROFFE was fatally injured in a mountaineering accident on Snowdon on February 12. While trying to reach by the quickest possible route a dying woman climber whose fall he had seen, he himself fell and was instantly killed. Anthony James Warren Woodroffe was the son of Mr. H. L. Warren Woodroffe, who is on the staff of the Chester Royal Infirmary. He was educated at Epsom College and Downing College, Cambridge. After completing his clinical studies at Liverpool he qualified in 1943, and almost immediately afterwards obtained a commission in the R.N.V.R. He was present at the D-Day landings in France as a surgeon-lieutenant in H.M.S. *Arethusa*. Later he served in the Mediterranean and Greece. After demobilization he became a house-physician at the Chesterfield and North Derbyshire Hospital and in 1947 graduated M.B., B.Chir. (Camb.). He returned to Chester and joined his father and Dr. W. M. Diggle in practice in the following year. In the short period in which he had been in practice in Chester he had already built up a reputation for professional ability and kindness to his patients. "Tony," as he was affectionately known to his many friends and colleagues, was popular with all and held high in their esteem, and his loss in such a tragic manner will be felt over a wide area around Chester. He was a keen mountaineer, and it is sad that he lost his life while having a few hours' relaxation after the rush of the influenza epidemic. It was typical of him that he should think of the welfare of others first, and it may be truly said that his life was given in the service of others. He leaves a wife, who is a doctor, and two young children, to whom our deepest sympathies are extended as well as to the other members of his family.—D. R. O.

Dr. A. G. ALEXANDER died in Surbiton on February 22, aged 76. Alfred Gahagan Alexander was born and brought up in Dublin, where he graduated M.D. in 1906. After holding an appointment as house-surgeon at Noble's Hospital in the Isle of Man, he became surgeon to the Dublin Medical Mission, and this was the beginning of a lifetime of devoted missionary service. From 1908 to 1913 he worked in Northern Nigeria with the Sudan United Mission. He was ordained a deacon in 1912, and a priest in 1913, and for a short time he held a curacy in Dublin. During the first world war he served in Egypt as a temporary major in the R.A.M.C. In 1919 he joined the staff of the Church Missionary Society and worked at the Society's Jaffa and

Hebron hospitals until 1928. He was then invited to become superintendent of the Birmingham Medical Mission, and for the next 13 years of his life he devoted all his energies to the sick poor around Floodgate Street and also in the neighbourhood of the new branch of the Mission at Lea Hall. As his assistant and successor at the Birmingham Medical Mission I fell heir to a vast fund of good will accumulated by Dr. Alexander, and I found that his irrepressible humour and unfailing courtesy were only the outward signs of a sterling Christian character. In 1910 he married Miss Isobel Milne, who has been one with him in all his activities. The sympathy of all their friends will go out to her and her two daughters, one of whom is a child-welfare specialist in Birmingham.—G. J. A.

Dr. JOSHUA WILLIAMSON, who was well known to many doctors in Lincolnshire, died on February 25 at Grimsby. He studied medicine at Leeds, graduating M.B., Ch.B. (Victoria University, Manchester) in 1898. Some years later, after the University of Leeds had been granted a charter, he also graduated at that university. After serving as senior house-physician and senior house-surgeon at the Leeds General Infirmary he started in practice in Grimsby. In spite of his early resolve that one week's stay there would suffice, he remained in practice in the area for 47 years. He was appointed an honorary consulting surgeon of the Grimsby General Hospital in 1905, and he gave devoted and skilful service there for many years. Williamson's progress in office in the B.M.A. was a pointer to the esteem in which he was held locally as the Association's activities progressed. He was president of the East Yorks and North Lincs Branch in 1922, chairman of the North Lincs Division in 1923, president of the Lincolnshire Branch from 1934 to 1935, and for a few months in 1934 chairman of the Grimsby Division. Privately he lived yesterday, to-day, and especially to-morrow to the full. He was a great Rotarian, with the idea of service always before self. He was a keen angler and good golfer, but it was in the field of music that Williamson really enriched the cultural soil of the district, and much of the latter's eminence in this sphere is due to his active participation as conductor and composer. His wife predeceased him by some 18 months. His friends and colleagues can look back with gratitude for having such a man so long in their midst.—E. A. R.

Dr. FRANK CROSBIE died suddenly on March 3 at his home in Cobh, County Cork, at the age of 61. A member of a well-known Kerry family, he graduated M.B., B.Ch., B.A.O. at Trinity College, Dublin, in 1911, where he won the essay prize of his year, and proceeded M.D. in 1912. After holding resident appointments at the Guest Hospital, Dudley, and the National Hospital for Consumption for Ireland, he joined the R.A.M.C. at the outbreak of the first world war, and served with the R.A.M.C. in France, the Balkans, and southern Russia, being mentioned in dispatches and retiring in 1920 with the rank of lieutenant-colonel. During the last war he was medical officer in charge of a civil defence mobile unit in West London. For many years a familiar figure on the lawn tennis courts at Wimbledon, he played in the All England championships from 1922 to 1937. In 1926 he won the close championship of Ireland. He was ten times Midland Counties champion, first in 1908 and most recently in 1938—a remarkable feat. Practically the whole of his professional life was spent in Ealing, where he was for some 25 years in general practice, and also until recent years an honorary medical officer to the King Edward Memorial Hospital in that borough. Ill-health forced him to give up private practice in 1948, when he retired to his native country. Crosbie was of literary tastes, an excellent conversationalist, and a good doctor; he was a man much beloved by his patients, a staunch and loyal friend to his colleagues, and an adornment to his profession. Our sincere sympathy goes to his widow, his daughter, and two sons, who are officers in the Royal Navy.—R. M. McK. and J. W. R. B.

Dr. ALICE PENNELL, who died suddenly at Findon, near Worthing, on March 7, was as distinguished a character as her late husband, Dr. Theodore Pennell, that great medical missionary of the North-West Frontier. She was one of the three famous Sorabji sisters, whose father, the Rev. Khardesi Sorabji, was among the first Parsee Christians. Alice Maud Sorabji graduated M.B., B.S. at the Royal Free Hospital in 1905. After her marriage to Dr. Pennell in 1908 she worked with him at Bannu Hospital until his death in 1912—an ideally happy partnership, though all too short. In 1913 Dr. Alice Pennell was accepted as a C.M.S. missionary and returned to Bannu, where she soon became a popular and influential figure among both Europeans and Indians. The Frontier tribespeople had a high regard for her, for her work as a doctor was outstanding. She founded the Victoria High School at Poona, which was carried on by her daughters for many years. For her service in military hospitals and elsewhere during the first world war she was three times mentioned in dispatches and appointed O.B.E. In 1918 she was awarded the Kaisar-i-Hind medal for her work on the North-west Frontier. Dr. Pennell retired from the C.M.S. in 1925 and took up residence in Chelsea, where she continued to practise as a doctor. She frequently lectured about India to British troops, and for many years she ran the Sisterhood of the Orient (later called the Sisterhood of the East and West) at Crosby Hall, where many of her distinguished British friends were introduced to Eastern visitors.

A friend writes: Alice Pennell was equally at home with a queen or a beggar—a great lady, proud and spirited like the Frontier folk whom she loved, a large-hearted friend and a devoted Christian.

Dr. RICHARD IRVINE POSTON died in Manchester Royal Infirmary on March 16 after a long illness. The youngest son of the late Robert Henry Poston, of Belfast, he was born in 1896 and educated at the Royal Belfast Academical Institution. One of the many medical students of the Queen's University who left its lecture-rooms to serve in the war of 1914–18, he joined the Royal Artillery and rose to the rank of captain before being demobilized to resume his studies. He was wounded while serving in Belgium in 1917. He graduated M.B., B.Ch., B.A.O. with first-class honours in 1922 and at once became assistant to Dr. G. Taylor, of Failsworth, Lancashire. In 1925 he studied the post-encephalitic patients in the practice and wrote an M.D. thesis on "Vestibular or Labyrinthine Epidemic Encephalitis" which was published in *Brain* in 1926. Dick Poston was a man of great and varied gifts and tremendous energy. As well as carrying out a large general practice he became surgeon to Oldham Royal Infirmary and to Boundary Park Municipal Hospital, and a certifying factory surgeon. He was an officer and an assistant commissioner of the St. John Ambulance Brigade, in which he maintained an active interest for 27 years. His lifelong enthusiasm was for the Territorial Army, and he rendered faithful service to it in peace and in war. After settling in practice he became battalion medical officer to the 9th Manchester Regiment, and in 1939 he took the 125th Field Ambulance to France and brought it, still functioning as a unit, through the nightmare of Dunkirk. After a period in command of No. 1 C.C.S. in the Isle of Man he went to North Africa in command of No. 97 General Hospital and served in that campaign, and later in command of the 69th General Hospital in the Italian campaign. He was invalided from the Army after fracturing his leg in 1944. On his retirement from active military service he became honorary colonel of the 7th Western General Hospital (T.A.) and of the 12th Western C.C.S., an honour which he had well earned. After demobilization he resumed practice in Failsworth and became vice-chairman of the Oldham Executive Council and a member of the Oldham and District Hospital Management Committee. He was also president of the local branch of the British Legion. Unfortunately his health gave rise to increasing anxiety, and it became obvious that he was

a sick man. Dick Poston was a staunch Ulsterman, a loyal son of "Queen's," and a great patriot. He "filled the unforgiving minute" with countless kindnesses to all sorts and conditions of men, and all too soon his happy warfare is accomplished. In 1922 he married Dr. Margaretta MacMillan, who practises as an anaesthetist, and their son is a medical student of St. Andrews University.—R. M.

Dr. ROBERT POTTER ELMER, of Wayne, Delaware, who died on March 4, aged 73, was an internationally known archer and honorary vice-president of the Royal Toxophilite Society. He contributed the article on archery to the *Encyclopaedia Britannica*, and his book on the subject was a standard work.

Medico-Legal

FINDING OF NEGLIGENCE AGAINST ANAESTHETIST

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In an action recently tried at Manchester Assizes[1] Mrs. Violet May Degg sued Dr. Aram Hovsep Kasasian for negligence. Mrs. Degg's case was that Dr. Kasasian, who gave the anaesthetic when she underwent an abdominal operation at the North Staffordshire Hospital, had injected the anaesthetic into an artery in her left arm instead of into the vein, with the result that the circulation in her arm was affected, and the limb ultimately had to be amputated below the elbow.

The evidence for the defence was that Mrs. Degg had not complained of intense pain when the injection was given, as she must have done had the needle been inserted in an artery, and that to pierce an artery the syringe would have had to be held at an angle rather than parallel to the arm.

In his summing up Mr. Justice Ormerod reminded the jury that on the issue of damages Mrs. Degg, a young woman of 34, had suffered a serious disfigurement which would last for the rest of her life, and had to wear a clumsy harness to support her artificial limb. On the issue of liability there was a direct conflict of medical evidence.

After the jury had found a verdict in favour of Mrs. Degg, and awarded £3,677 damages, Mr. Justice Ormerod gave judgment for that amount with costs, but granted a stay of execution for 21 days to give Dr. Kasasian an opportunity to consider whether to appeal.

[1] *Hanley Evening Sentinel*, March 2.

An interesting skin disease occurring among labourers in the pineapple-canning factories of South Malaya is reported in *Nature* of March 17, p. 442. It affects the palmar surfaces of the fingertips and the periphery of the palms, especially where there is slight pressure in grasping the fruit to cut it up. The skin becomes sore, with small superficial raw areas, which usually heal in a few days with an altered skin said to be bluish white and so smooth as to leave no finger-prints. Occasionally, usually in the skin folds, deep cracks occur which remain raw and bleeding for a long time. In Californian fruit-canning factories yeasts are responsible for skin lesions on the workers' hands, but in the present report the damage appears to be due to a protein-digesting enzyme, bromelin, present to the extent of 0.16% in the fresh pine-apple juice. The author suggests that similar skin damage by enzymes may be found to occur in those who work in slaughter-houses or are engaged in gutting mackerel, where proteolytic enzymes may be liberated from damaged tissues. It is also possible that bromelin could be usefully used in the histological laboratory for cleaning or altering tissue sections, and as a tool in research on the formation of keratin.

Medical Notes in Parliament

Prescribing

On March 15 Mr. GEOFFREY COOPER inquired what steps were taken to encourage medical practitioners and hospitals to use equivalent remedies in preference to patent medicines, and what was the estimated value of patent remedies still being prescribed under the Health Service.

Mr. MARQUAND answered that all doctors, both in general practice and in hospitals, had been asked to prescribe in accordance with the recommendations of the Joint Committee on Prescribing. He was consulting the British Medical Association on the question what further information or advice would be helpful to doctors. The information requested in the second part of the question was not available.

Doctors and Population

In a written answer the Minister of Health gave the following figures showing the population in certain towns and the doctors there giving general medical services under the National Health Service, including assistants where known:

	Population (June 30, 1950)	Doctors (January 1, 1951)
Bath	77,040	40
Blackpool	149,600	65
Southend-on-Sea	151,400	60
Salford	177,700	66
Oldham	119,500	43
Leicester	287,200	120
Eastbourne	58,040	38
Hastings	65,670	44
Sunderland	178,000	58
Southport	85,490	47
Leeds	509,400	238

X-ray Examinations for Miners

On March 19 Mr. E. H. C. LEATHER asked whether a scheme for an annual *x*-ray examination of all miners was being introduced.

Mr. PHILIP NOEL-BAKER replied that the National Joint Pneumoconiosis Committee had decided to start an experimental scheme which would serve as guidance for any general plan. Meanwhile, all miners diagnosed as having pneumoconiosis, including many thousands still at work, were being periodically re-examined, and 50,000 other miners had been examined by miniature radiography under the National Health Service.

Mr. LEATHER suggested that such schemes had already proved practicable in other countries, and said that it was important to follow up the splendid work being done by the Pneumoconiosis Research Unit.

Mr. NOEL-BAKER said they would certainly give the scheme top priority.

Dr. CHARLES HILL suggested that some of the existing mass radiography facilities should be diverted to this work from their present employment.

Mr. NOEL-BAKER pointed out that the Ministry of Health was represented on the Committee, but there was division of opinion among the experts on whether mass miniature radiography could detect pneumoconiosis in its early stages.

Teaching at Cardiff

On March 21 Mr. DAVID LLEWELLYN suggested the establishment of a national dental school for Wales in conjunction with the 1,000-bed teaching hospital to be established at the Heath, Cardiff.

Mr. H. MARQUAND said he would be glad to consider any proposals submitted.

Previously, on March 19, Mr. MARQUAND had stated that the governors of the United Cardiff Hospitals had been

advised that their proposed extension must await the completion of another scheme of higher priority.

Admission for Chronic Sick

On March 22 Mr. S. PRESCOTT asked whether Mr. Marquand was aware of the difficulty experienced by medical practitioners in obtaining admission to hospital for the chronic sick and that many deaths had resulted directly from the failure to obtain hospital accommodation for such persons.

Mr. A. BLENKINSOP answered that he knew that over the country as a whole there was a serious shortage of beds for the chronic sick. This could be finally cured only by the provision of additional beds, but Mr. Marquand was meanwhile considering a number of measures which he hoped will alleviate the position.

Spa Treatment

On March 23 Mr. B. JANNER reported that Harrogate was cutting spa fees to private patients as a result of the influx of National Health patients, who had brought prosperity to that spa. He asked how far other spas similarly benefited by the Health Service.

Mr. H. MARQUAND said that the regional hospital board concerned had contractual arrangements with the authorities responsible for the Harrogate spa and that similar arrangements had been made elsewhere, where reasonable terms could be secured and the treatment was regarded as medically valuable. The general jurisdiction and management of spas were outside his control.

Divorce.—Mr. Attlee has decided to recommend to His Majesty the appointment of a Royal Commission to review the law relating to divorce.

Westminster Hospital.—The site of the old Westminster Hospital was bought by the Government for £405,000.

Chemists' Pay.—Mr. Marquand, on March 15, refused to consider the appointment of a committee to inquire into the average earnings of pharmacists within the Health Service. He said remuneration of chemists was under review by the appropriate Whitley Council.

Sheep Carcasses.—Asked what is done with the carcasses of sheep after they have been used for the manufacture of vaccine lymph, Mr. Marquand states that producers of the lymph are responsible for getting rid of the carcasses. These are unsuitable for disposal to the meat trade.

Extra Rations.—Regional Food Officers have no authority to grant extra rations except under the direction of the Minister of Food. On medical matters the Ministry of Food is advised by a Special Diets Advisory Committee of the Medical Research Council. Their advice in a case raised by Dr. Reginald Bennett on March 14 was that extra rationed food was not necessary for any of the conditions mentioned in the medical certificate.

Dental Trade Prices.—Mr. Marquand said on March 15 that he hoped to lay before the House within the next few days an Order under Section 10 of the Monopolies and Restrictive Practices (Inquiry and Control) Act, 1948. He hoped that elimination of the practices which at present restricted competition in the dental trade would result in a reduction of prices.

Dental Schools.—The annual intake of dental schools in the years 1946, 1947, 1948, 1949, and 1950 respectively, was 641, 654, 662, 611, and 606.

Nurses from Overseas.—It is not possible to say how many nurses recruited from overseas are at present employed or in training in hospitals. In 1950 about 600 women, including about 350 student nurses, were recruited under official schemes in Germany, Persia, Italy, and the Colonies, while 564 men and women were transferred from the Irish Republic. In addition over 900 individual permits were issued for aliens to take up nursing employment or training in this country.

Age at Death.—The average age at death in Great Britain in the years 1939 and 1945 was 59 and 60 respectively. The provisional figure for 1949 was 64.

Opticians' Pay.—Fees for sight-testing accounted for £4,719,847 in the financial year 1949–50. Separate figures are not available for optical dispensing fees and the cost of supplying appliances, but the estimated apportionment is £8,800,000 and £8,200,000 respectively.

Consumption of Liquid Milk.—From October, 1950, to March, 1951, inclusive, this is provisionally estimated at 779 million gallons in the U.K. Comparable figures for the winters of 1949–50 and 1948–9 are 755 million gallons and 725 million gallons.

N.H.S. in Wales.—The total gross cost in 1949–50 was £19,602,000; the estimate for 1950–1 is £20,364,000.

The Services

AUXILIARY R.A.M.C. FUNDS

The annual general meeting of the members of the Auxiliary Royal Army Medical Corps Funds will be held at 11, Chandos Street, London, W., on Monday, April 9, at 5 p.m., to receive the report and accounts, to appoint officers, and to consider and, if thought fit, pass the following resolution: "That the administration of the Auxiliary Royal Army Medical Corps Funds be handed over to the Royal Army Medical Corps Fund, to be administered in accordance with the Trust Deed of 1916 and objects of the 1939 Fund, representation of the interests concerned being secured on the appropriate central committee."

A *Supplement* to the *London Gazette* has announced the following awards:

Four Clasps to the Territorial Efficiency Decoration.—Colonel H. F. Humphreys, O.B.E., M.C., T.D., R.A.M.C., retired.

Three Clasps to the Territorial Efficiency Decoration.—Colonel J. F. O'Grady, T.D. (Honorary Colonel 42nd (East Lancashire) Divisional R.A.M.C., T.A.), and Colonel M. H. Summers, D.S.O., T.D., R.A.M.C.

Two Clasps to the Territorial Efficiency Decoration.—Brigadier A. L. Crockford, D.S.O., O.B.E., M.C., T.D., K.H.S., Colonel W. W. Crawford, T.D. (now S.R., R.A.M.C.), Lieutenant-Colonels M. W. Gonin, D.S.O., T.D., and A. H. D. Smith, M.C., T.D., retired, Major (Honorary Colonel) E. Walsh, T.D., retired, and Majors R. E. M. Fawcett, T.D., and K. W. N. Palmer, T.D., R.A.M.C.

First Clasps to the Territorial Efficiency Decoration.—Colonel R. W. Nevis, T.D., R.A.M.C.

Territorial Efficiency Decoration and Two Clasps.—Lieutenant-Colonel G. L. Malcolm-Smith, R.A.M.C.

Territorial Efficiency Decoration and First Clasp.—Major (Honorary Lieutenant-Colonel) W. P. Purvis, R.A.M.C.

Territorial Efficiency Decoration.—Colonel R. F. Guymer, Lieutenant-Colonel H. L. Sheehan, Major (Honorary Lieutenant-Colonel) C. K. Colwill, Major C. H. Pauli, and Captain (Honorary Major) F. C. O'Mara, R.A.M.C.

Universities and Colleges

UNIVERSITY OF OXFORD

In Convocation on March 14 A. G. McD. Weddell, M.D., Fellow of Oriel College, was admitted to office as Senior Proctor for the ensuing year.

UNIVERSITY OF GLASGOW

During the five hundredth anniversary celebrations of the founding of the University of Glasgow in June a number of honorary degrees will be conferred, including that of LL.D. on Professor Dorothy S. Russell, M.D., F.R.C.P., professor of morbid anatomy in the University of London and director of the Bernhard Baron Institute of Pathology at the London Hospital.

UNIVERSITY OF DUBLIN

Professor J. Harold Burn, M.D., F.R.S., professor of pharmacology in the University of Oxford, has been appointed John Mallet Purser Lecturer for 1951. It is hoped that Professor Burn will deliver the lecture on "The Importance of *Nor*adrenaline," in Trinity College, Dublin, on Wednesday, May 9.

UNIVERSITY OF DURHAM

Ernest Farquhar Murray, M.D., F.R.C.S., F.R.C.O.G., Professor of Midwifery and Gynaecology from 1935 to January this year, when he retired from the Chair, has had the title of Emeritus Professor conferred upon him by the University.

UNIVERSITY OF LONDON

The Langley Memorial Prize, value £21, is open to competition among officers of the Colonial Medical Service who are serving, or who have served, in West Africa. The prize will be awarded for the best paper submitted on a topic falling within one of the following subjects, special consideration being given to original work: (*a*) tropical medicine or surgery; (*b*) tropical hygiene and sanitation; (*c*) tropical entomology and parasitology. Papers, which may consist of either published or unpublished work, should be delivered to the Dean, London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1, not later than November 1.

UNIVERSITY OF SHEFFIELD

At a special degree Congregation to be held on July 12 the honorary degree of Litt.D. will be conferred on Geoffrey Langdon Keynes, M.D., F.R.C.S., Emeritus Surgeon at St. Bartholomew's Hospital and Vice-President of the Bibliographical Society of London.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College, held on February 8, with Sir Cecil Wakeley, President, in the chair, a Past-President's Badge was presented to Sir Holburt Waring.

Charles David Read, F.R.C.S.Ed., F.R.A.C.S., F.R.C.O.G., was elected to the Fellowship of the College *ad eundem*.

Mr. J. M. Wyatt was reappointed representative of the College on the Central Midwives' Board.

Professor H. H. Stones was appointed Charles Tomes Lecturer for 1951. It was reported that Dr. Loyal Davis (Chicago) would deliver a Moynihan Lecture on October 9. The Hallett Prize was presented to Mr. M. W. Reece (St. Thomas's Hospital).

The Council decided that the first award of the James Berry Prize would be made in 1952. The subject for essays will be "The Treatment and Preservation of the Injured Hand."

The following hospitals were recognized under paragraph 23 of the Fellowship regulations for the posts specified: Royal United Hospital, Bath (one registrar, one house-surgeon to ear, nose, and throat department); Selly Oak Hospital, Birmingham (surgical registrar, for one year, and first, second, and third house-surgeons, for six months); Black Notley Hospital, Braintree (resident surgical officer, general house-surgeon, orthopaedic house-surgeon, for six months); Hereford County Hospital (surgical registrar, for one year, house-surgeon, for six months); Lewisham Hospital (two general registrars, one orthopaedic registrar, for one year, senior house-surgeon, junior house-surgeon, for six months); St. Mary's Hospital, Portsmouth (senior surgical registrar, surgical registrar, for one year, general house-surgeon, general and orthopaedic house-surgeon, for six months); St. Albans City Hospital (two surgical registrars, for one year, two house-surgeons, for six months); Royal Albert Edward Infirmary, Wigan (surgical registrar, for one year, two house-surgeons, casualty officer, orthopaedic house-surgeon, orthopaedic registrar, for six months).

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a ceremony held in the College on March 14 with Mr. W. Quarry Wood, President, in the chair, the following were admitted Fellows in Dental Surgery without examination: J. Aitchison, *A. B. P. Amies, D.D.Sc., F.R.C.S.Ed., D.L.O., F.R.A.C.S., F.R.S., *A. J. Arnott, *W. Balendra, M.R.C.S., L.R.C.P., L.D.S., G. A. Ballantyne, J. Boyes, F.R.C.S.Ed., L.D.S., A. J. Brown, F.R.C.S.Ed., L.D.S., T. R. Calder, J. R. J. Cameron, F.R.C.S.Ed., L.D.S., *E. Charron, *H. M. Crombie, M.B., Ch.B., L.D.S., A. Cubie, J. W. Daunt, *V. Desai, T. H. J. Douglas, F.R.F.P.S., F.D.S., *R. C. S. Dow, L.R.C.P.&S.Ed., L.D.S., H.D.D., E. S. Friel, F. G. Gibbs, F.R.C.P.Ed., F.R.C.S.Ed., L.D.S., A. D Hitchin, A. P. Husband, A. C. W. Hutchinson, J. D. H. Jamieson, C. H. Kemball, *E. Lapira, W. R. Logan, L.R.C.P.& S.Ed., L.D.S., H.D.D., *S. F. Lumb, J. Lyons, *K. McGrath, M.B., B.Ch., B.D.S., *A. Macgregor, D. MacGregor, A. G. Mackay, W. F. Mackenzie, M.B., Ch.B., F.R.F.P.S., L.D.S., D. S. Middleton, F.R.C.S.Ed., L.D.S., A. E. Miller, *C. F. Mummery, T. Rankin, C. Read, F.R.F.P.S., L.D.S., D. L. Rogers, *A. E. Rowlett, *M. A. Rushton, M.D., L.D.S., *H. R. Shah, H. M. Sturrock, L.R.C.P.&S.Ed., L.D.S., W. R. Tattersall, E. K. Tratman, *J. P. Walsh, D.D.Sc., M.B., B.S., F.D.S., J. F. Webster, F.R.F.P.S., L.D.S., *F. R. P. Williams, J. T. Wood.

*In absentia.

CONJOINT BOARD IN SCOTLAND

The following candidates, having passed the final examination, were admitted L.R.C.P.Ed., L.R.C.S.Ed., and L.R.F.P.&S.Glas. on March 9: Patricia F. D. Anderson, J. Boyd, G. McG. Campbell, C. MacP. Christie, G. Clarke, D. M. Cunningham, A. de Mello, J. Y. N. Devine, J. A. Eykelenboom, Hannah Furman, J. Goldie, A. E. D. J. Hellegers, D. W. Kidd, Ruth Kope, June M. Litt, J. T. Lunn, R. Martin, J. Minsky, M. H. Pinsky, T. Rice, June Rosin, W. S. Thompson.

CONJOINT BOARD IN IRELAND

The following candidates were duly admitted licentiates in medicine and midwifery on March 16, having passed the final examination in medicine, surgery, and midwifery of the Conjoint Board in Ireland: D. B. Barnett, P. B. Carvill, W. F. Clifford, J. L. Davidson, E. Fischer, J. C. Grogan, P. D. McCarthy, E. S. McDaniel, P. McGovern, Dympna MacNamara, Margaret M. J. O'Dea, I. Ryan, D. White.

Vital Statistics

Influenza

The influenza epidemic of this year has been the worst since 1933, when the maximum weekly deaths in the great towns numbered 1,934, compared with 1,269 in the present outbreak. The severity and length of the local outbreaks have varied considerably between the great towns. The present outbreak first appeared in Newcastle-upon-Tyne and then in Liverpool and the neighbouring large towns. In the former area the maximum number of deaths occurred in the week ending January 6, while in the latter area the maximum occurred a week later. Generally the outbreaks appeared earlier in the North, with the exception of Yorkshire, than in the remainder of the country. The large cities of London, Birmingham, and Glasgow had relatively a light mortality experience. The death rates for the past 13 weeks for the towns with the largest number of deaths are shown in the Table below:

Influenza in the Great Towns: Annual Death Rates Per 10,000

Town	December			January				February				March		Total Deaths
	16	23	30	6	13	20	27	3	10	17	24	3	10	
Newcastle ..	2	14	18	62	55	12	12	4	11	5	5	—	11	116
Leeds ..	—	—	1	1	13	24	27	33	23	7	10	5	1	141
Sheffield ..	—	2	—	—	1	8	19	30	26	11	13	4	1	115
Bradford ..	4	4	2	2	5	11	34	34	36	21	12	16	4	103
Blackburn ..	5	5	5	5	9	19	89	154	51	23	23	5	5	85
Birkenhead ..	—	4	—	51	154	84	40	22	4	—	—	4	—	99
Blackpool ..	—	—	—	18	7	102	88	42	39	14	14	—	—	92
Bootle ..	—	—	7	52	37	163	44	22	7	—	—	—	—	45
Liverpool ..	—	1	10	58	140	94	39	16	12	6	3	2	5	598
Manchester ..	—	1	1	11	16	33	53	32	23	9	8	4	1	259
Preston ..	—	—	—	9	17	69	52	87	22	9	4	4	4	64
Southport ..	6	6	12	73	91	109	85	30	36	6	—	—	6	76
St. Helens ..	—	—	5	135	232	107	42	28	14	32	14	5	—	132
Wallasey ..	—	—	15	169	257	236	72	41	—	21	—	15	5	162
Wigan ..	12	—	6	—	98	153	79	85	31	12	6	12	18	84
Leicester ..	—	—	—	2	13	24	62	51	31	20	13	2	5	122
Nottingham ..	5	2	2	2	2	3	26	39	32	27	12	3	9	96
Wolverh'ton ..	3	3	—	3	3	29	84	68	52	16	6	3	—	84
Birmingham ..	1	—	1	2	6	12	25	35	23	14	11	6	3	297
Coventry ..	2	2	—	—	4	24	41	18	22	8	14	2	4	70
Stoke-on-Trent	—	—	2	—	8	26	76	60	45	25	21	8	6	146
Norwich ..	—	—	4	4	9	22	69	78	87	13	48	—	4	78
Cambridge ..	—	6	—	—	—	17	68	114	51	51	23	—	17	62
Bristol ..	5	1	1	5	7	18	48	42	36	22	7	5	7	174
Cardiff ..	2	4	—	6	4	30	25	40	25	8	6	8	2	77
Swansea ..	—	3	—	—	—	29	78	65	45	42	13	—	6	87
London ..	0·3	0·6	1	6	12	16	19	22	12	8	3	3	2	689
Glasgow ..	1	—	1	4	16	24	18	14	5	2	2	1	0·5	185
Belfast ..	—	1	—	9	39	70	40	13	3	8	7	2	2	178
Dublin ..	—	—	—	—	1	18	52	35	20	9	8	3	2	166

Week Ending March 17

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,007, whooping-cough 5,516, diphtheria 50, measles 31,837, acute pneumonia 1,106, acute poliomyelitis 18, dysentery 1,672, paratyphoid fever 5, typhoid fever 1. Deaths from influenza in the great towns numbered 88.

Infectious Diseases

During the week ending March 10 decreases were recorded in the number of notifications of whooping-cough 459, acute pneumonia 225, and measles 87, while rises were recorded for scarlet fever 106 and dysentery 85.

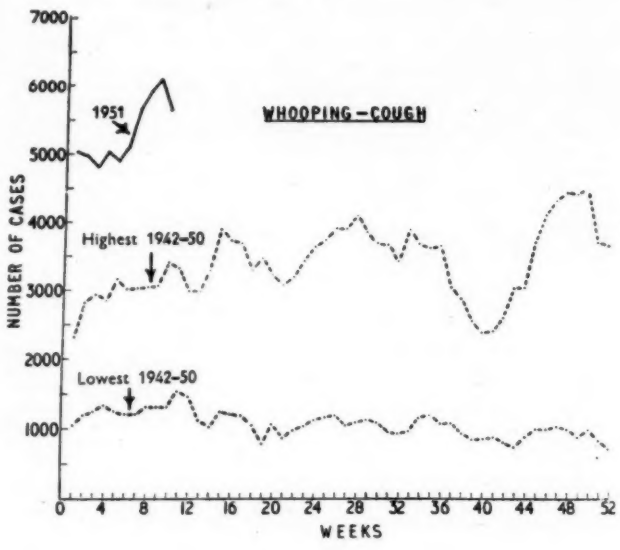
With the exception of the preceding week the number of notifications of measles was the largest ever recorded. There were large increases in Staffordshire 373, Essex 267, London 186, and Gloucestershire 166, while the largest fall was in Yorkshire West Riding 429. The decline in the incidence of whooping-cough was mainly confined to the northern section of the country, the largest decreases being Lancashire 126 and Yorkshire West Riding 106. The increased incidence of scarlet fever was mainly due to the experience of three counties—Surrey 36, Middlesex 28, Essex 24—while only small variations occurred in the trends of other areas. No fluctuations of any size occurred in the local returns of diphtheria.

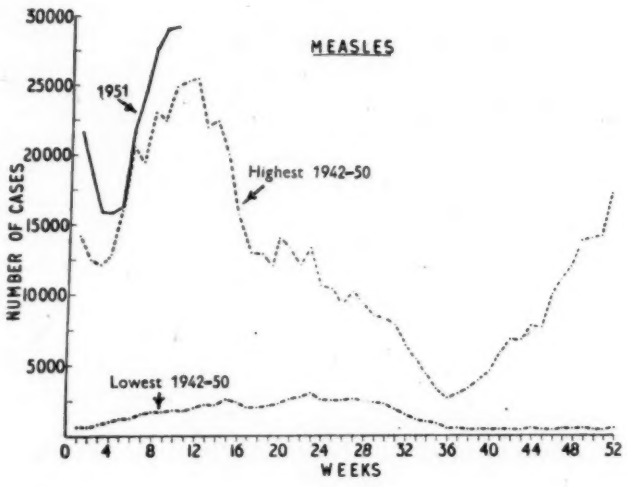
The notifications of acute poliomyelitis were 15 fewer than in the preceding week and were the lowest total for 94 weeks. The only areas with multiple notifications were Lancashire 4 (Liverpool C.B. 2) and Essex 2.

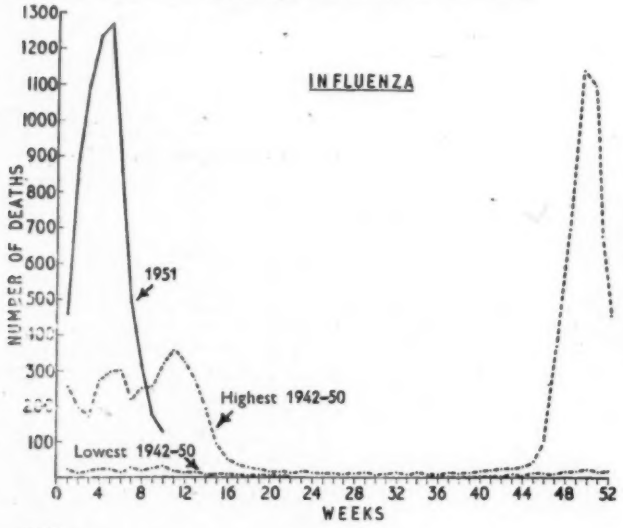
The notifications of dysentery were the largest of recent years. Two fresh outbreaks were reported during the week in Cambridge (Cambridge M.B. 54) and Lincolnshire (Scunthorpe M.B. 22). The largest rises during the week were in London, from 133 to 181, and in Essex, from 92 to 145. The other very large returns were Lancashire 201 and Middlesex 153.

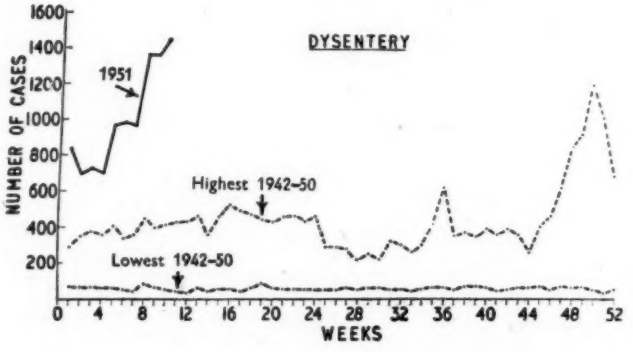
Graphs of Infectious Diseases

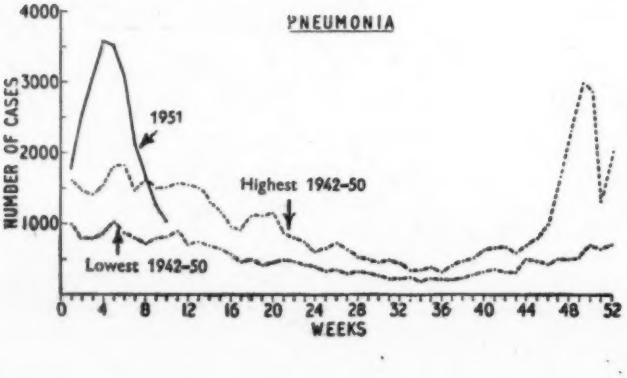
The graphs below show the uncorrected numbers of cases (deaths from influenza) of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - -, the figures for 1951 thus ———. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

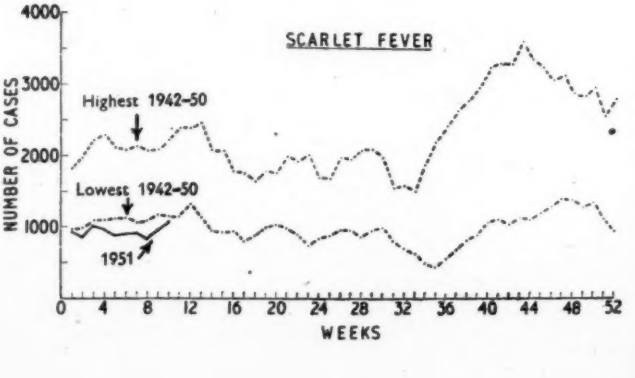












INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending March 10 (No. 10).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county) (*c*) Scotland (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending March 10					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	46	3	18	—	2	62	8	19	1	2	837	472	62
Deaths	—	—	1	—	—	—	—	—	—	—			
Dysentery	1,449	181	297	16	3	362	11	90	—	2	412	208	49
Deaths		—		—					—				
Encephalitis, acute	3	1	—	—		4	—	—	—	—	5	1	—
Deaths		—			—		—						
Erysipelas			15	3	8			22	10	10			
Food-poisoning	89	8		—		50	3		—				
Infective enteritis or diarrhoea under 2 years				24	28					13			
Deaths	14		2	2	1	18		3	—	2			
Measles*	29,067	3,501	359	93	89	5,476	60	195	439	68	25,049	8,449	1,672
Deaths		1	1	–	—			—	—	1			
Meningococcal infection	44	4	19	1	2	27	1	18	2	2	227	77	27
Deaths		1	—				1	—					
Ophthalmia neonatorum	48	3	20	—	1	34	3	13	—		88	57	34
Pneumonia, influenzal	1,027	51	13	14	16	1,014	60	26	26	—	1,514	1,014	813
Deaths (from influenza)†	130	13	3	3	4	108	14	14	2	—			
Pneumonia, primary			233					292					
Deaths	297	46		9	12	355	68		16	10			
Poliomyelitis, acute:													
Paralytic	9	—	1	1	1	41	3	4	—	6	41	10	5
Non-paralytic	4	—											
Deaths§	2	—			—	2	1			—			
Puerperal fever			6				—	7					
Puerperal pyrexia‖	86	9	9	1		106	11	3	—		194	128	95
Scarlet fever	1,056	53	165	36	61	2,093	123	176	127	77	2,215	1,424	1,137
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			180	31				199	28				
(2) Tuberculosis, non-respiratory			22	6				42	6				
(1) Deaths	184	18	18	4	11	209	32	36	8	11			
(2) Deaths		7	6	2	2		4	7	—	4			
Typhoid fever	11	2	2	—	—	4	1	1	1	3			
Deaths¶	—	—	—	—		—	—	—	—		24	8	3
Paratyphoid fever	4	—	1 (B)	—		8	—	1 (B)	—				
Whooping-cough	5,637	420	806	56	105	1,917	77	361	53	73	3,418	1,506	1,323
Deaths	9	1	1	—	—	3	1	—	1	—			
Deaths (0–1 year)	303	31	34	11	21	301	37	48	12	15	636	410	301
Deaths (excluding stillbirths)	6,310	1,030	714	146	245	6,081	937	722	151	195	7,755	5,770	5,053
Annual death rate (per 1,000 persons living)			14·4					14·5					
Live births	7,453	1,268	911	207	417	7,837	1,274	946	222	399	9,650	7,534	5,962
Annual rate per 1,000 persons living			18·4					19·0					
Stillbirths	206	23	33			216	27	28			290	241	171
Rate per 1,000 total births (including stillborn)			35					29					

* Measles not notifiable in Scotland and returns are approximate † Includes primary form for England and Wales, London and N. Ireland § The number of deaths from polioencephalitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Medical News

"Family Doctor"

At a reception on Monday, March 19, Dr. E. A. Gregg, Chairman of Council, welcomed the Minister of Health, Mr. Hilary Marquand, and representatives of the Press who had been invited to celebrate the launching of *Family Doctor*. Dr. Gregg referred sympathetically to the many difficulties in the way of those publishing a new magazine in these days of shortage of materials and high costs. He then asked Mr. Marquand if he would follow him in giving *Family Doctor* his support. Mr. Marquand said that he was very pleased that this new journal has been established. "I wish it all success, and particularly so because I read one sentence in Dr. Clegg's introductory letter which seemed to me to strike the keynote of the new journal and which I hope it will continue to maintain. He said the title *Family Doctor* for this health magazine may help to emphasize that the doctor's main concern is to make and keep people well. A journal launched in that spirit has my fullest possible support." It continued the spirit in which the National Health Service was established three years ago. They should remember that the important job was to make and keep the people well. "We must, in other words, act together, using all our powers to educate the people in the necessity for health and to encourage them to co-operate with the service of the general practitioner in the maintenance of health." There was an enormous lot of work to be done in this field, and he thought that *Family Doctor* set out to do it. It set out to educate the public, to explain to the public, and to seek the co-operation of the public with their best friend, the family doctor, in maintaining the health of their families. "So I think," Mr. Marquand concluded, "this journal starts under very happy auspices. I hope it will be successful. I believe it is sincerely intended by the B.M.A. as a gesture of co-operation in a great national endeavour to make and keep the people well; and as that, I think, is what it is, I have no hesitation whatever in giving it my support. I hope it will flourish. I hope it will be widely read, and that it will be of very great value to all the people."

"The Bonesetter of Crosshall Street"

The Liverpool Playhouse is giving the first performance on April 3 of this play about Evan Thomas, the father of Hugh Owen Thomas, the pioneer of modern orthopaedic surgery, the central theme being the struggle between quackery and orthodox medicine. The author is Dr. W. Hywel Jones, a Welsh general practitioner who qualified at University College Hospital in 1935.

Wigs

The conditions for which wigs may be prescribed in the National Health Service have been more closely defined in a recent circular (R.H.B. (51) 21) from the Ministry of Health. Now wigs may be prescribed only when the baldness is due to congenital dystrophy of the skin, or alopecia totalis, or alopecia areata (severe and long-standing), or to extensive scarring following trauma, *x*-ray application, or an inflammatory condition. As before, a second condition must also be fulfilled—namely, that the wig is considered necessary by a hospital specialist.

Slimming by Television

On Thursday of last week Lord Horder was asked by the B.B.C. to explain by television why it was inadvisable for those overweight to attempt to slim without the advice of their doctors. In giving his audience sensible help on this question Lord Horder took the opportunity of reminding them that general practitioners are now exceptionally busy. The medical profession will applaud this wise decision of the B.B.C. and its public-spirited action in deciding not to distribute the diet sheets.

Helping the R.A.M.C.

The Supplementary Reserve for the Army has recently been reconstituted. It provides the technical and administrative units which are the essential complement to the Territorial Army but raised essentially on a skill or trade basis and not by region. In the case of the R.A.M.C. the call is for pharmacists, dispensers, laboratory assistants and operating theatre assistants, radiographers, nursing orderlies, and the like, and the peacetime liability is only an annual 15-day camp, since those who volunteer for the Supplementary Reserve perform in peace the kind of duties they will be asked to do in war. Full information can be obtained from any Army recruiting office.

Wills

Dr. Ernest Bosdin Leech, consulting physician to the Manchester Royal Infirmary, a keen antiquarian, and son of Sir Bosdin Leech, Lord Mayor of Manchester, 1891–2, and one of the promoters of the Manchester Ship Canal, left £31,462. Dr. George Henkell Drummond Robinson, formerly well known in London as a specialist in midwifery and diseases of women, left £15,505.

COMING EVENTS

Institute of Psychiatry

The Institute of Psychiatry (University of London) has announced that lectures and demonstration courses for post-graduate students in psychiatry will be given at the Maudsley Hospital, Denmark Hill, London, S.E., third term commencing on April 2. The courses have been arranged for first- and second-year students, and will include the following subjects: historical development of modern psychiatry, principles of dynamic psychology, systematic general psychiatry, including treatment, pathology of the central nervous system, biochemistry in connexion with the central nervous system, clinical applications of the electroencephalogram, forensic psychiatry, psychiatry and the community, and criminology. Further details may be obtained on application to the Institute.

Medical Art Society

The annual exhibition is open free to the public, April 2 to 14, at Walker's Galleries, New Bond Street, London, W.1. The Society's annual general meeting and dinner is at Kettners Restaurant at 6.15 p.m. on Monday, April 2, to be followed by the private view of the exhibition.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

INSTITUTE OF ACTUARIES.—At Chartered Insurance Institute, 20, Aldermanbury, London, E.C., April 2, 5 p.m., "*Group Life and Pensions Schemes, including Group Family Income Benefit Schemes*," by Mr. G. W. Pingstone.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—April 2, 5.30 p.m., lecture demonstration by Dr. E. Stengel.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN, 17, Bloomsbury Square, London, W.C.—April 2, 7.30 p.m., "*The Work and Problems of a Coroner*," by Dr. W. Bentley Purchase.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—April 2, 5 p.m., "*Medical Ophthalmology*," by Professor Arnold Sorsby.

Tuesday

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 3, 5.30 p.m., "*Some Recent Views on the Diagnosis and Treatment of Ocular Palsies in Cases of Exophthalmic Ophthalmoplegia*," by Mr. T. K. Lyle.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 3, 5 p.m., "*Raynaud's Phenomenon—A Review of the Clinical Problem*," Hunterian Lecture by Professor R. P. Jepson.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—April 3, 5 p.m., "*The Refracting Media: Accommodation Retinoscopy*," by Dr. T. H. Whittington.

Wednesday

GLASGOW UNIVERSITY: DEPARTMENT OF OPHTHALMOLOGY.—April 4, 8 p.m., *"Ascorbic Acid and Corneal Lesions,"* by Dr. T. A. S. Boyd.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 4, 3.45 p.m., *"Tubercle of Bone,"* Erasmus Wilson Demonstration by Mr. P. H. Mitchiner.

●ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W., April 4, 3.30 p.m., *"The Common Cold,"* by Dr. C. H. Andrewes, F.R.S.

SOCIETY OF PUBLIC ANALYSTS.—At Chemical Society, Burlington House, Piccadilly, London, W., April 4, 7 p.m., papers by (1) J. Hubert Hamence, M.Sc., Ph.D., F.R.I.C., (2) E. I. Johnson and J. King, O.B.E., F.R.I.C., and (3) J. A. Kitchener, Ph.D., A. Liberman, B.Sc., Ph.D., D.I.C., and D. A. Spratt, B.Sc., A.R.C.S.

Thursday

FACULTY OF HOMOEOPATHY, Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C.—April 5, 5 p.m., *"Experiences in Recent Influenza Epidemic,"* by Dr. James Hamilton; *"Observations on Influenzal Complications and Their Treatment,"* by Dr. C. O. Kennedy. Discussion to be opened by Dr. Hector MacNeill.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 5, 5.30 p.m., *"Some Aspects of the Pathology of Fat,"* by Mr. E. Wolff.

QUEEN'S UNIVERSITY (GREAT HALL), Belfast.—April 5, 8.30 p.m., *"A Medical Survey of the Irish Famine of 1846,"* Robert Campbell Memorial Oration by Sir William MacArthur (postponed from January 11).

SOCIETY OF ENDOCRINOLOGY.—At Royal Society of Medicine, 1, Wimpole Street, London, W., April 5, 5.30 p.m., *"Studies on A.C.T.H. and Cortisone in Disease,"* by Professor J. S. L. Browne (Montreal).

Friday

BIOCHEMICAL SOCIETY.—At Department of Physiology, University of Bristol, Bristol, April 6, 2 p.m., 296th meeting. Papers will be read.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 6, 5.30 p.m., *"The Ophthalmological Aspects of Disseminated Sclerosis and Allied Diseases,"* by Dr. S. Behrman.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 6, 5 p.m., *"Diagnosis of Stone in the Urinary Tract,"* Urology Lecture by Mr. F. J. F. Barrington.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, London, E.—April 6, 8.30 p.m., *"The Action of Carcinogenic Chemicals on the Skin,"* by Dr. M. H. Salaman.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Alexander.—On March 10, 1951, to Mary (formerly Stubbs), wife of David F. Alexander, M.B., Ch.B., D.R.C.O.G., Stratton St. Margaret, near Swindon, Wilts, a daughter.

Collins.—On March 13, 1951, at the General Infirmary, Burton-on-Trent, to Violet, wife of Dr. W. Collins, a son.

Perrott.—On March 17, 1951, at Fernwood House, Newcastle-upon-Tyne, to Nancy (formerly Hodgson), wife of Dr. John William Perrott, twin sons.

Playfair.—On March 21, 1951, at Cambridge, to Margaretta, wife of Dr. A. S. Playfair, a daughter—Anthea.

Smith.—On February 14, 1951, at Preston, to Dr. Kathleen Smith (formerly Turner), wife of Irvine Smith, F.R.C.S., a daughter—Anne.

Smithson.—On March 12, 1951, to Harriet (formerly Gregson), wife of Dr. R. G. Smithson, of Wetherby, Yorks, twin sons.

Tate.—On March 12, 1951, at Mansfield Nursing Home, to Margaret, wife of Malcolm Tate, B.M., a brother for Philip—Alan.

Waldron.—On March 9, 1951, at Bristol, to Laura, wife of Dr. E. A. Waldron, 124, Pembroke Road, Bristol, a son.

DEATHS

Cromie.—On March 15, 1951, at Surbiton, Surrey, Mortimer John Cromie, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired, aged 70.

Crowe.—On March 2, 1951, at Witney, Oxon, George Arthur Crowe, L.M.S.S.A., aged 80.

Dalgliesh.—On March 11, 1951, William Dalgliesh, M.B., Ch.B., of Hillrise, Witney, Oxon, aged 70.

Eatough.—On March 15, 1951, Robert Eatough, M.D., late of Mossley, Manchester, aged 88.

Gibson.—On March 20, 1951, at The White House, Aldershot, John Hutchinson Gibson, M.R.C.S., L.R.C.P., aged 92.

Hirst.—On March 18, 1951, at Southmead Hospital, Bristol, Geoffrey Greatrix Hirst, M.R.C.S., L.R.C.P., Lieutenant-Colonel, I.M.S., retired, formerly of Heath House, Finchampstead, Berks, aged 72.

Jack.—On March 14, 1951, at his home, 67, Forest Road, Aberdeen, William James Jack, M.B., Ch.B., late of Adlington, Lancs, aged 54.

Kryszek.—On March 15, 1951, at Kota Kota, Nyasaland, Monica Margaret Kryszek (formerly Renner), M.B., Ch.B.

Lundie.—On March 20, 1951, at Dundee Royal Infirmary, Alexander Lundie, M.B., Ch.B., D.P.H., of 25, Charlotte Street, Dundee.

Milne.—On March 21, 1951, at Greystones, Witham, Essex, Charles Milne, O.B.E., M.B., C.M., Colonel, I.M.S., retired, aged 81.

Mitchell.—On March 19, 1951, at "Three Trees," Dukes Wood Drive, Gerrard's Cross, Bucks, Godfrey William Mitchell, M.D., D.P.H., D.M.R.E., aged 65.

Oliver.—On March 21, 1951, at the Brighton General Hospital, Matthew James Oliver, M.B., C.M., D.P.H., of Hove, Sussex.

Sandoe.—On March 15, 1951, at "Greenbank," Bodmin, Cornwall, John Worden Sandoe, M.D., aged 89.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Rh Antibody and Precautions at Confinement

Q.—*Is it safe for an Rh-negative mother, whose husband is Rh-positive, to be delivered of her second child in a nursing-home where there are no facilities for blood-typing or for transfusion? The first child was normal in every respect. Maternal blood tests during the 30th and 34th weeks of the present pregnancy showed no rhesus antibodies.*

A.—If no Rh antibody is present in the mother's serum at the 34th week of pregnancy it is still possible that the antibody may develop during the last six weeks. However, experience shows that Rh antibody which is detected for the first time during the last few weeks of a pregnancy never causes severe signs in the infant, and in the great majority of cases the infant pursues an entirely normal course. Accordingly, if a test at 34 weeks shows that no Rh antibody is present it may be assumed that the infant is not going to need treatment, and the infant can safely be born in a place where there are no facilities for blood typing or for transfusion.

Sensitization to a Plastic Eye

Q.—*I have a patient, a boy of 8, who wears an artificial eye. It is found that when he wears a plastic eye the socket becomes inflamed and discharges. Could this be an allergic reaction to the plastic, and, if so, is there any test, in the nature of a patch test, which could be carried out to discover if it is, in fact, the plastic which is responsible?*

A.—The simplest test whether a discharge from a socket is due to a plastic shell is to change the plastic shell for one of glass or porcelain. Some sockets tend to become inflamed with any artificial eye, but provided the socket is well healed this should be readily amenable to control. There is, however, no doubt that some patients do not tolerate plastic shells, just as a number of people develop contact dermatitis from plastic spectacles. J. Macivor (*Canad. med. Ass. J.*, 1950, **62**, 164) reported eight cases of contact allergy in a series of 100 patients with an artificial eye. In two of these eight cases there was a plastic implant and the remaining six patients wore plastic artificial eyes. The patch test on the forearm with a powdered polymer and liquid monomer of methyl methacrylate gave a positive result for the polymer in 96 hours in three cases, and in a fourth case the test was positive for both polymer and monomer. In the remaining four cases the skin patch test was negative to both, but in all cases the insertion of a small button of clear plastic in the socket produced a typical allergic response. In these eight cases the removal of the plastic implant or the substitution of a glass eye for a plastic artificial eye cleared the symptoms.

Treatment of Raynaud's Disease

Q.—*What recent advances have there been in the treatment of Raynaud's disease? What is considered the best treatment for this condition?*

A.—Recent changes in the treatment of Raynaud's disease have been directed to the search for an effective vasodilator drug the effect of which would be of sufficient duration to be of real value for a constitutional disease, and which would not have unpleasant secondary effects. At present 2-benzyl-4:5-imidazoline hydrochloride ("priscol") offers the nearest approach to these requirements.

The best treatment for Raynaud's disease is to go and live in a warm climate, or at least to follow an occupation in which work is done in warm surroundings. For those who must live in a cold climate and who suffer only slight disability, warm clothing and active exercise may suffice, with priscol as an adjuvant in cold spells. For the more severe cases sympathectomy usually provides substantial relief of symptoms, though it is difficult or impossible to tell beforehand which patients will derive the greatest degree of benefit from the operation.

Vitamin A, Influenza, and the Common Cold

Q.—*Is there any evidence that vitamin A is a good prophylactic or treatment for influenza or the common cold?*

A.—One of the most prominent lesions in experimental vitamin-A deficiency is usually a xerosis of the mucous membranes, including those of the upper respiratory tract, and infections are often superimposed. It might be expected, therefore, that substantial doses of vitamin A would help to prevent influenza and colds. Most of the trials in which groups of normally nourished volunteers have been dosed with extra vitamin A, however, have failed to demonstrate that any benefit is derived. No trials appear to have been made on the value of vitamin-A therapy in reducing the severity of the catarrh and coughs which so frequently follow colds.

Is there a Safe Period?

Q.—*I have been asked to give evidence in court on the following matter: a young man has been accused of being the father of a child. He has denied this, and the girl in question has taken him to court. In the course of her evidence the girl has stated that she had intercourse with the accused on the fifth day of her period. Normally her periods last six or seven days. This is all the intercourse she admits. Is conception possible as a result of coitus during a menstrual period?*

A.—Although conception is unlikely except when intercourse takes place between the 10th and the 18th days of a 28-day cycle, there is evidence that pregnancy has sometimes resulted from single acts of intercourse on any day of the cycle. If, therefore, in this case intercourse is admitted at any time, paternity cannot be said to be impossible. The cycle is not stated, but, if this is less than 28 days, then the chance of pregnancy from coitus on the fifth day would be greater than usual. The fact that the girl was still menstruating at the time does not affect the issue.

Booster T.A.B.

Q.—*I received the usual T.A.B. inoculations five years ago. What is necessary to bring my immunity up to a satisfactory level now?*

A.—The original course of T.A.B. vaccine should have established a good basal immunity. If the inquirer is going to an area where typhoid is common, or wishes to have his immunity boosted for any other reason, he needs only one additional dose of 0.5 ml. of T.A.B. vaccine. He should, however, remember that artificial immunization does not guarantee complete protection, and all hygienic precautions should be taken against the risk of enteric infections.

Pros and Cons of Spinal Analgesia

Q.—*What are the principal indications and contraindications for spinal analgesia?*

A.—Spinal analgesia is used by some for pain relief alone when other methods of analgesia would be either less safe or less efficient. The burly seaman who is to have, say, a hernia repaired is an example, for such a patient may tax the resources of the anaesthetist if simple inhalation anaesthesia is chosen. Spinal analgesia is more usually indicated when profound muscular relaxation is necessary for the operation and when it is considered that this state cannot be produced more safely by other means. This indication includes the whole field of extensive abdominal and pelvic surgery in fit patients, although the former supremacy of this method is now challenged by the relaxants.

There are two general contraindications to a spinal. One is any difficulty or uncertainty in providing perfect asepsis of the patient's skin or the instruments. The other is any anxiety about the general state of health of the patient. Spinal analgesia has its best use in the robust. Many other more specific contraindications to spinal analgesia have been given, but the following meet with fairly general agreement: (1) Patients who have a large abdominal tumour which restricts movement of the diaphragm. Superimposed intercostal paralysis here may lead to grave respiratory difficulty. (2) Extensive lung disease contraindicates the method, because respiratory efficiency is inevitably lowered by spinal analgesia. These patients are better off with general anaesthesia, where temporary respiratory difficulty can be countered by the anaesthetist. (3) Patients with a past history of coronary disease or angina are poor subjects for high spinal analgesia on account of the fall in blood pressure. An E.C.G. which reveals myocardial damage should preclude spinal analgesia. (4) The low blood pressure likely to occur during a spinal probably precludes this method in patients with poor excretory function. The patient suffering from latent uraemia may not be able to afford to exist for one or more hours without kidney function.

Boiled or Raw, Sir?

Q.—*Which is more digestible—a raw egg or one lightly boiled?*

A.—Cooked eggs appear to be more readily digested than raw eggs, which tend to escape digestion in the stomach and to pass unchanged into the duodenum. The value of raw eggs in feeding patients unable to retain other food probably depends on their small activity in stimulating the digestive processes of the stomach. In work with rats raw egg-white has been found to contain avidin, an antivitamin which immobilizes biotin and causes skin lesions and a characteristic hunched attitude. Some caution may therefore be necessary if large quantities of raw egg have to be given to patients over long periods. At the present stage of our knowledge, however, theoretical considerations should not perhaps be allowed to influence methods of giving eggs which have been found by long-established practice to give satisfactory results. There would seem to be no good reason either to give raw eggs to patients capable of eating an ordinary diet or to refrain from giving them to those who are unable to tolerate other forms of food.

Pigeon Chest

Q.—*How may the development of pigeon chest with Harrison's sulcus be prevented? Is there any treatment for the deformity once it has developed?*

A.—The cause of pigeon chest is uncertain. Many still believe that it is due to rickets or respiratory obstruction. If it is due to rickets, the method of preventing and treating the condition—namely, by vitamin D—is obvious. Brodkin (*Pediatrics*, 1949, **3**, 286), however, has presented evidence that it is due to a congenital abnormality in the attachment of the diaphragm. If this is the case, prevention is impossible, and no treatment is likely to be of value.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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